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# FAT EMBOLISM

## INCLUDING EXPERIMENTAL PRODUCTION WITHOUT TRAUMA *

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Since the discovery of free neutral fat in the blood vessels following injury, the subject of fat embolism has been widely investigated clinically and experimentally. As may so easily happen when an apparently direct and unequivocal cause-effect relationship is presented, the search for other causes has been overlooked; and this, in spite of the fact that the more familiar we become with fat embolism, the less unequivocal the commonly accepted etiology appears. This article is the record of an attack on this unsettled problem from a new direction.

A detailed review of the literature of fat embolism need not be given here. It has been thoroughly covered in English by Warthin (1913 [1]) and in German by Landois (1923 [2]), Paul and Windholz (1925 [3]) and others.

We need only summarize those facts on which complete agreement exists among most authors, and in somewhat more detail discuss those observations that cast doubt on the sufficiency for all cases of the ordinary etiologic explanation.

In the first place, it is essential to make clear what we mean by fat embolism. The normal blood, even in digestive lipemia, contains no free neutral fat in droplets large enough to take the fat stains. Following injury to bone marrow and in certain other conditions to be emphasized later, free neutral fat can under the microscope be demonstrated in the blood stream by staining methods. This is the essence of the definition. The occurrence of symptoms or of death from the presence of this free neutral fat then becomes a question of quantity and distribution. A

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1. Warthin: Internat. Clin. **4**:171, 1913.
2. Landois: Ergeben. d. Chir. u. Orthop. **16**:99, 1923.
3. Paul, F., and Windholz, F.: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **38**:614, 1925.

definition that requires demonstration of an actually plugged capillary does not seem useful to us for reasons that will appear later. If there is microscopic (as opposed to ultramicroscopic) free fat in the blood stream, a sufficient agglomeration of particles may occur anywhere and at any time to plug a capillary.

The general problem of fat embolism, then, must be divided into two main divisions. The first of these concerns itself solely with the sources of free neutral fat in the blood stream and the mechanisms of its appearance there. The second deals with the results of this entrance of fat into the blood stream as expressed by pathologic and clinical changes. It must therefore take into consideration quantity, distribution and composition of the fat introduced.

## PART I. ETIOLOGY OF FAT EMBOLISM

There is no doubt that depot fat, particularly that of the marrow, will enter the blood stream following mechanical disturbance. Hundreds of cases demonstrating this fact are on record, as may be seen by reference to the reviews of the subject already mentioned. The types of mechanical injury include fracture, operations on soft parts and on bone, and severe concussion of the body. Traumatic etiology can be readily demonstrated experimentally.[4] Mechanical disturbance of marrow fat, experimental fracture, jarring of bones, experimental bone transplants, in fact, all procedures leading to any appreciable damage to fat depots are regularly accompanied by the appearance of intravascular fat in varying quantities and by resulting degrees of capillary occlusion. To confirm these findings we have successfully repeated certain of these experiments (figs. 1, 2 and 3). The lung embolism seen in figure 1 appeared in the brief interval between the occurrence of multiple fractures of the skull and death in a dog. Figures 2 and 3 show the embolism present in the lungs of rabbits six hours after destruction of the bone marrow of a single femur under ether anesthesia. The degree of embolism in these instances is to be kept in mind for comparison with later experimental results.

The ease and logic of this explanation for certain examples of fat embolism have misled those interested in the problem. Time and again in the literature of the subject the statement is made that trauma is the only possible cause of fat embolism. Examples of these statements are the following: "In order to permit the entrance of fat into the circulation in amounts even to approach the amount of free fat in the blood

4. Busch: Arch. f. path. Anat. **35**:321, 1866. Ribbert: Cor. Bl. f. schweiz. Aerzte **24**:457, 1894. Fritzsche: Deutsche Ztschr. f. Chir. **107**:456, 1910. Bergemann: Berl. klin. Wchnschr. **47**:1112, 1910. Bissell, W. W.: Surg. Gynec. Obst. **25**:8 (July) 1917. Caldwell, G. T., and Huber, H. L.: Surg. Gynec. Obst. **25**:650 (Dec.) 1917.

stream in pulmonary fat embolism, there must first be injury to the fatty tissue and, second, a break in the continuity of the blood stream." [5] "Fat embolism is an acute circulatory disturbance caused by trauma." [6] "The cause is always trauma." [6] "Fat in the minute particles of emulsification or saponification plays little if any important rôle in the production of embolism." [7] Evidence is not produced to support these statements.

There is no question of the occurrence of traumatic fat embolism, but there is equally no question that trauma is not the only cause of fat embolism. The following observations recorded in the literature of the

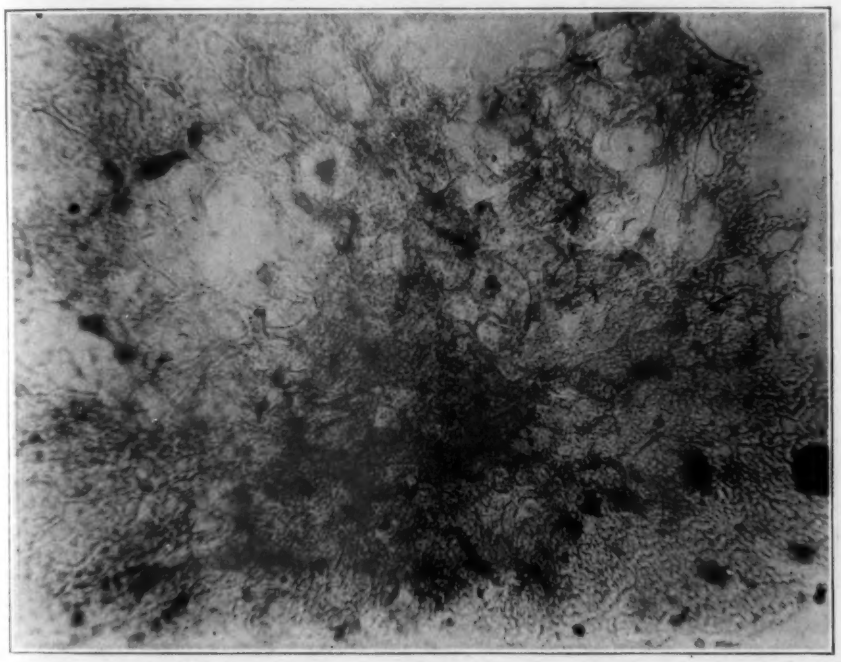

Fig. 1.—Experimental traumatic fat embolism: lung section (sudan III) from dog following multiple skull fractures.

subject demonstrate the inadequacy of the traumatic conception to cover all cases.

Carrara [8] reports fat embolism present at necropsy in 22 per cent of deaths from cardiovascular-renal disease and in 44 per cent of burns. Catsaras [9] found fat emboli in the lungs in eighteen of sixty-seven cases

5. Sutton, G. E.: Ann. Surg. **76**:581 (Nov.) 1922.
6. Gauss, H.: Pathology of Fat Embolism, Arch. Surg. **9**:593 (Nov.) 1924.
7. Elting, A. W., and Martin, C. E.: Ann. Surg. **82**:336 (Sept.) 1925.
8. Carrara: Friedreich's Bl. f. gerichtl. med. **49**:, 1898, cited by Warthin (footnote 1) and Gröndahl, Deutsche Ztschr. f. Chir. **111**:56, 1911.
9. Catsaras, J.: Presse méd. **28**:618 (Sept. 4) 1920.

of postinfluenzal pneumonia. Gröndahl [10] reports fat embolism in two cases of eclampsia, four cases of diabetes, and two cases of phosphorus poisoning; Winkler [11] in two cases of acidosis, and Winogradow [12] as occurring regularly in potassium chlorate poisoning. In addition to these repeated findings there have been authentic reports of fat embolism having occurred, without history of trauma, in one or more cases of each of the following conditions: carbon monoxide poisoning,[8] profound sepsis,[10] chronic alcoholism,[10] chloroform narcosis,[11] diabetic retinitis,[13] phlegmonous gastritis,[10] acute pancreatitis,[8] chronic tuberculosis,[8] menstrual suppression, hepatitis, splenitis, carcinomatosis and sarcomatosis.[1] (The last five conditions are cited from the literature by Warthin.)

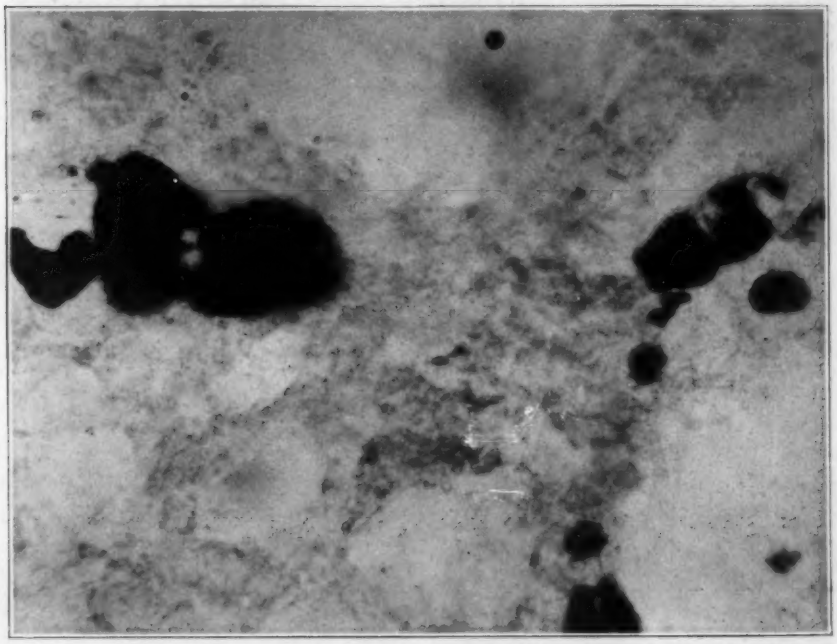

Fig. 2.—Experimental traumatic fat embolism: lung section (high power, sudan III) from rabbit killed six hours after destruction of bone marrow of a single femur.

For the sake of convenience we can group most of these varying conditions under four main heads: (1) metabolic disturbances (diabetes, cardiovascular-renal syndrome); (2) poisonings; (3) toxemias from acute infections, and (4) toxemias from tissue destruction (burns).

10. Gröndahl (footnote 8).
11. Winkler: Ztschr. f. orthop. Chir. **45**:616, 1924.
12. Winogradow: Virchows Arch. f. path. Anat. **190**:92, 1907.
13. Bantin, C. F.: Diabetic Lipemia Retinalis and Fat Embolism, J. A. M. A. **86**:546 (Feb. 20) 1926.

(It must be remembered that marked tissue destruction is also present in many cases of fat embolism that are ascribed to traumatic origin.) These diverse types of disease have in common only the very general element of marked chemical and physical alterations of the blood.

From these observations it becomes clear that (1) fat embolism is a not infrequent finding at postmortem in a variety of conditions; (2) in many conditions in which it has been observed trauma has played no part; (3) those nontraumatic conditions in which it has occurred are largely associated with chemical or physical changes in the blood.

Fig. 3.—Experimental traumatic fat embolism: lung section (low power, sudan III) from similar experiment to that shown in figure 2.

A further fact may be here noted, namely, that in fatal traumatic fat embolism, the amount of fat found in the capillaries is sometimes disproportionately great to the amount of depot fat actually disturbed by the injury. Warthin [1] states, "There is no clinical correspondence between the apparent injury and the degree of the resulting lipemia." Elting and Martin state,[7] "The amount of fat which may, and in fatal cases is deposited in the capillaries is apparently out of proportion to what would be regarded as the normal amount of fat in the traumatized area. Some observers have thought that there must be some other source for the free fat, but none has as yet been demonstrated."

*Trauma, therefore, is not the cause of all fat embolism, nor as a corollary is the free fat found in cases associated with trauma necessarily all due to the trauma itself.*

Before proceeding to experimental results that may cast some light on the questions (1) from what other sources than depot fat and (2) by what other mechanism than trauma does neutral fat appear in the blood, it will be well here to suggest a thought that will color the succeeding argument. If such other source can be proved, and such other mechanism can be demonstrated, then it becomes possible that any case of traumatic fat embolism except those fatal within a few minutes may possess a double etiology. The importance of this conception becomes clear in reviewing Porter's [14] work on fat embolism and shock. He believed that the shock state could be initiated by fat embolism, and he observed fat embolism in patients dead of shock. Now shock of a certain type may be regarded as an intoxication with products of tissue destruction. If fat embolism can occur from chemical changes in the blood (as the review above suggests) then the embolism observed may be the result of shock rather than its cause.

We present experimental evidence suggesting that (1) there is an obvious source of fat in fat embolism, other than depot fat—one that has been dismissed by numerous authors with mention only—namely, the ultramicroscopic emulsion of fat in the normal blood plasma; (2) the mechanism by which this physiologic emulsion is coarsened so that droplets are found of a size capable of producing embolism is that already suggested, namely, physical or chemical changes in the blood.

The physiologic occurrence of fat in the blood plasma varies greatly with the state of nutrition. It occurs in ultramicroscopic particles seen in the dark field as refractile bodies that exhibit active Brownian movement.[15] The number of these in the organism starved for twenty-four hours is very small; under such circumstances it is sometimes almost impossible to find one in many fields. Following a rich fat meal, however, they crowd every field so intensely as to make a perceptible increase in the amount of light that is refracted into the observer's eye. Quantitative fat determinations show physiologic variations in blood fat content in man from 0.2 to 2 per cent and in the dog from 0.1 to 2 per cent.[16] In man under pathologic conditions it may rise as high as 26 per cent.[13] This fine emulsion is the result of resynthesization of the fed fat that has been hydrolyzed in the intestine. It is presumed to be stabilized by soaps formed from fatty acids also originating from the fed fat in the process of hydrolysis.

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14. Porter, W. T.: Boston M. & S. J. **176**:248 (Feb. 15) 1917; ibid. **177**:326 (Sept. 6) 1917; Am. J. Physiol. **71**:277 (Jan.) 1925.

15. Neumann: Centralbl. f. Physiol. **21**:102, 1907. Gage, S. H., and Fish, P. A.: Am. J. Anat. **34**:1 (Sept.) 1924.

16. Leathes and Raper: The Fats, London, 1925, p. 144.

Fischer and Hooker,[17] in prefacing their interesting speculations on fatty degeneration, studied the formation of emulsions. The problem that faced us in regard to the origin of fat emboli from normal plasma fat was one of the breakdown of emulsions. Such a study led to interesting and suggestive results.

Emulsions are the simplest types of colloids and have been largely used, therefore, for the study of colloid behavior. They consist of two phases, an external and an internal phase, that is, the medium in which a substance is emulsified and the substance so emulsified. There is also the interphase, which is the term applied to the multiple surfaces separating the two phases. In certain emulsions this interphase is occupied by a film of a colloid such as soap. The stability of the emulsion depends on the difference in surface tension between the external and the internal phase. This, in turn, is a matter of ionic concentration on the respective surfaces, and varies inversely with the size of the emulsified droplets. In emulsions held by a colloid, it depends on the integrity of the colloid film.

From this brief consideration of the theory of emulsions it becomes evident that (1) an alteration in surface tension relationship and (2) an attack on the interphase are the two logical methods of attempting breakdown of emulsions. Dessication and other processes associated with changes of ionic concentration are the commonest examples of the former method. Precipitation of a potassium soap film with calcium salts is an example of the latter. Emulsions of oil in water will break down under treatment with a fat solvent. In addition, we have found certain reagents to be active in the breakdown of emulsions, the nature of whose action is unexplained. It is probable that these substances, histamine, peptone, necrotic muscle extract, etc., act by altering surface tension. We have in view certain experiments on surface tension to determine this point.

### IN VITRO EXPERIMENTS

We have used three emulsions which we will designate A, B and C.

A. An ordinary emulsion of olive or cottonseed oil in water made in the proportions of 75 cc. of oil to 25 cc. of water with from 4 to 5 cc. of potassium soap added as the emulsifying agent. This emulsion is made by fractional grinding of the oil into the water in a mortar. It is fairly stable. Less than 5 per cent of the oil will separate out on standing for five days (fig. 4). Under the microscope it shows fat droplets varying from 2 or 3 microns up to large globules filling the field.

B. This emulsion differs from A only in the fineness of the droplets. It is made of olive oil and water in the same proportion but it is ground under pressure by a machine made for commercial preparation of emul-

17. Fischer and Hooker: Fats and Fatty Degeneration, New York, 1917.

sions (Premier mill). It is stable over months. Under the microscope it shows a much smaller average size of droplets. There are even ultramicroscopic dancing refractile bodies such as have been described in the blood plasma.

C. This is the physiologic emulsion of blood serum described as occurring after a fat meal. Dogs were fed a pint of cream and bled at the end of one and one-half to two hours. The blood was immediately defibrinated, the corpuscles removed by centrifugalization, and the creamy serum used. The gross appearance of the serum was the only guide to the degree of lipemia.

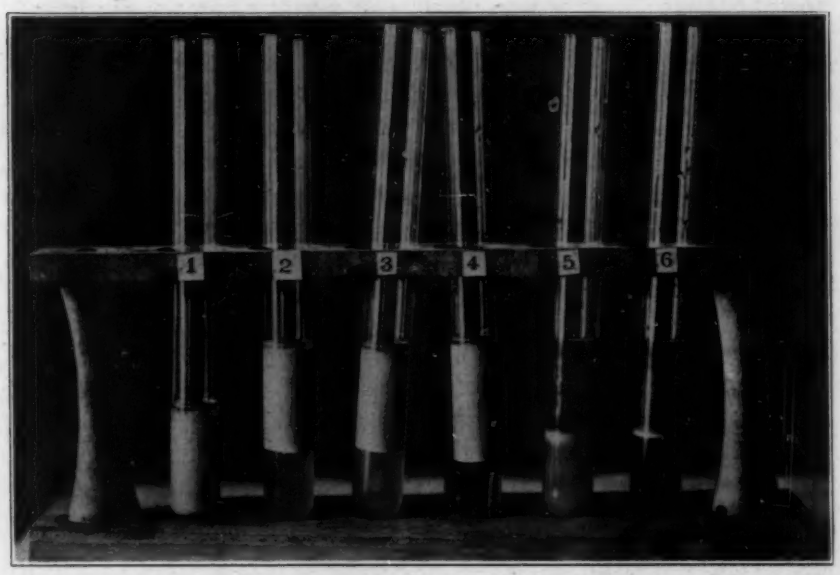


Fig. 4 (experiment 9).—Emulsion A, 5 cc., treated with reagents as follows: tube 1, none; tube 2, 3 cc. of tap water; tube 3, 3 cc. of 0.7 per cent sodium chloride solution; tube 4, 3 cc. of saline extract of fresh muscle; tube 5, 3 cc. of saline extract of necrotic muscle; tube 6, 3 cc. of same extract as tube 5, rendered alkaline to litmus. Complete breaking down of emulsion by necrotic muscle extract should be noted; photographed at ninety hours.

Differences in the behavior of these three emulsions to various agents occurred, as will be seen hereafter.

Each series of breakdown experiments was controlled by tubes containing the untreated emulsion, and dilutions of the emulsion with tap water and physiologic sodium chloride solution. In no instance in which the emulsion was properly made did more than a minimal freeing of the oil occur in these controls. Only satisfactorily controlled emulsions were recorded.

EMULSION A (FIGS. 4 TO 9)

Reasoning *a priori* from the fact that many cases of the late appearance of the symptoms of fat embolism are also cases in which there is marked destruction of soft tissue, an early tentative experiment was made, using an extract in physiologic sodium chloride solution of necrotic muscle, controlled by a similar extract of fresh muscle. The result of this experiment, often repeated since, was amazing to us (fig. 4). The extract of necrotic muscle caused immediate and complete breakdown of the emulsion, whereas all the controls remained unchanged.

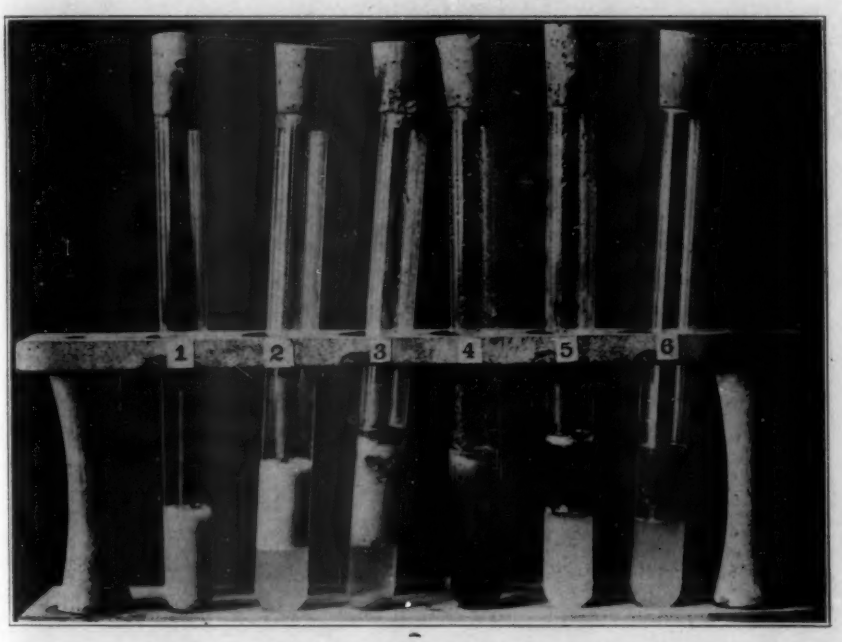


Fig. 5 (experiment 13).—Emulsion A, 5 cc., treated with reagents as follows: tube 1, none; tube 2, 3 cc. of tap water; tube 3, 3 cc. of saline extract of necrotic muscle; tube 4, 3 cc. of blood serum of dog dead of intestinal obstruction; tube 5, 3 cc. of commercial pancreatin; tube 6, 3 cc. of fresh pancreatic juice of dog; photographed at ninety hours.

With this striking result as a beginning, a number of different substances were studied, some with direct relationship to the problem at hand and to the first result, and some as available substances that might afford interesting observations. The results, given below (figs. 4 to 9), are based on many observations, except when otherwise stated, with varying concentrations and amounts of the reagents.

*Fat Solvents.*—Ether and alcohol if present in excess will dissolve out the oil in the emulsion.

*Soap Precipitants.*—Calcium lactate, magnesium sulphate, manganese chloride, cobalt nitrate and all soluble salts of the heavy metals will displace the potassium in the emulsifying soap and precipitate an insoluble soap. There is rapid clearing of the oil in a solid layer on the surface.

*Acids and Alkalis.*—On the basis of only a few observations, it is probable that marked variations in acidity in either direction will free the fat in this emulsion. A volume of tenth normal hydrochloric acid or sodium hydroxide added to an equal volume of emulsion is moderately effective.

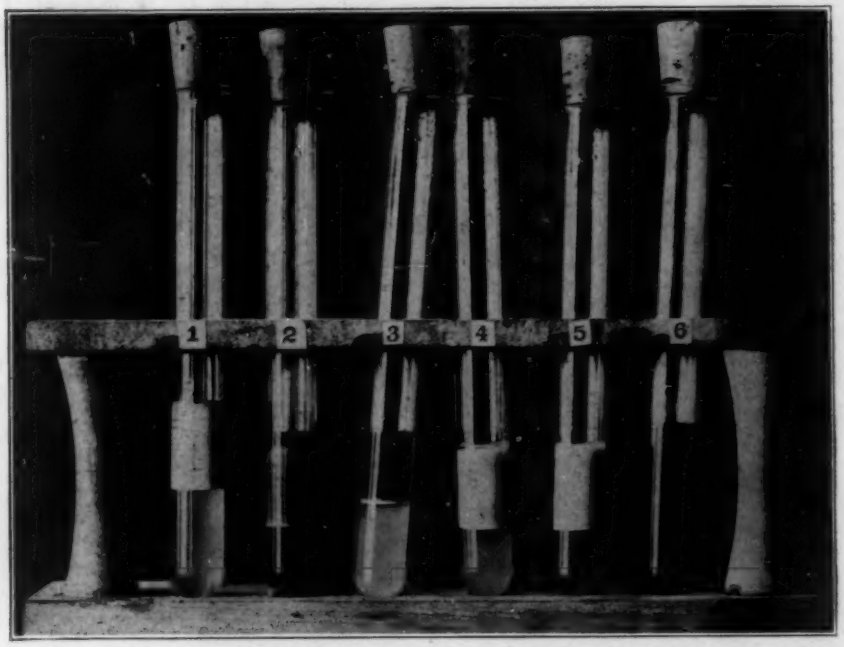


Fig. 6 (experiment 19).—Emulsion A, 5 cc., treated with reagents as follows: tube 1, 5 cc. of tap water; tube 2, 3 cc. of 1 per cent hemoglobin solution; tube 3, 3 cc. of 0.1 per cent histamine solution; tube 4, 3 cc. of 1 per cent sodium glycocholate solution; tube 5, 3 cc. of 1 per cent sodium taurocholate solution; tube 6, 3 cc. of fresh dog bile. Tube 3, treated with histamine, shows complete breakdown of emulsion, which occurred in a few seconds; photographed at forty-eight hours.

*Products of Protein Decomposition.*—Necrotic Muscle: The extract in physiologic sodium chloride solution of autolyzed muscle could, of course, not be calibrated. The muscle was autolyzed in vivo by aseptic isolation or in vitro, and was ground in a mortar with the salt solution. The mixture was filtered through gauze, forming a foul, brown, turbid liquid. The effect of this extract was uniformly prompt and positive. One failure was recorded. The reaction of the extract was rendered alkaline to litmus and methyl red with sodium hydroxide without alteration of its property of breaking the emulsion.

Peptone: Commercial peptone ("bacteriologic") was used in a 1 per cent solution. It appeared somewhat less efficient than either necrotic muscle extract or histamine, but definite freeing of oil never failed to occur.

Histamine: The instantaneous and complete breakdown of this emulsion by histamine in dilution of 0.2 per cent and even of 0.1 per cent is striking. Three cubic centimeters of histamine 0.1 per cent solution added to 5 cc. of emulsion frees all the oil before inversion of the tube can be completed (fig. 6). This observation is constant in many

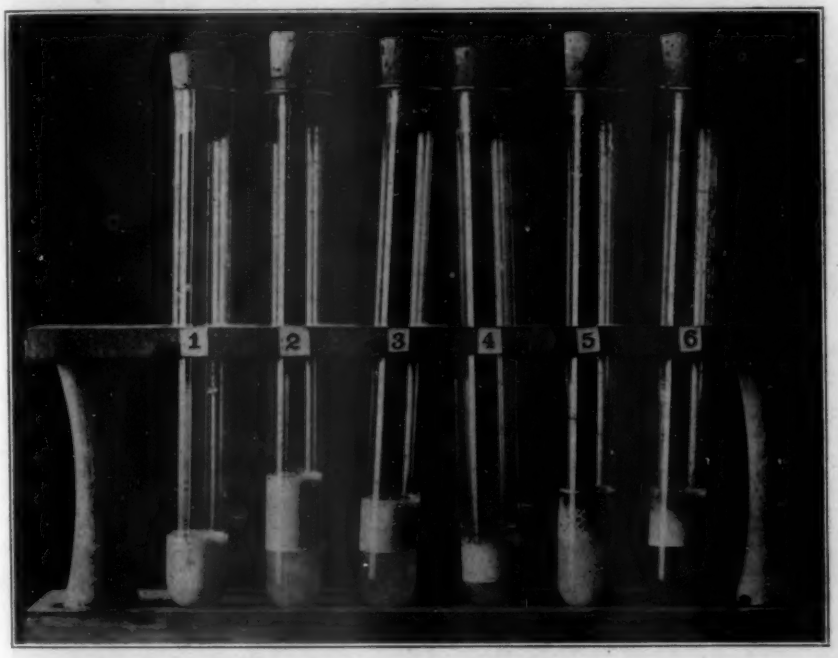


Fig. 7 (experiment 22).—Emulsion A, 3 cc., treated with reagents as follows: tube 1, none; tube 2, 3 cc. of tap water; tube 3, 3 cc. of 0.7 per cent sodium chloride solution; tube 4, 1 cc. of 1 per cent peptone solution; tube 5, 3 cc. of 1 per cent peptone solution; tube 6, 3 cc. of 1 per cent saponin. Photographed at twenty-four hours.

repetitions. The reaction of the histamine solution may also be varied on both sides of neutral (to methyl red) without effect on this property.

Hemoglobin: We group hemoglobin here because it is probable that the samples we used were partially decomposed with the consequent presence of histamine. The solutions had a definitely foul odor. The action was not constant, but at least partial breakdown of the emulsion came to be expected. It is interesting to observe that fresh hemoglobin as represented in fresh muscle extracts apparently had no effect.

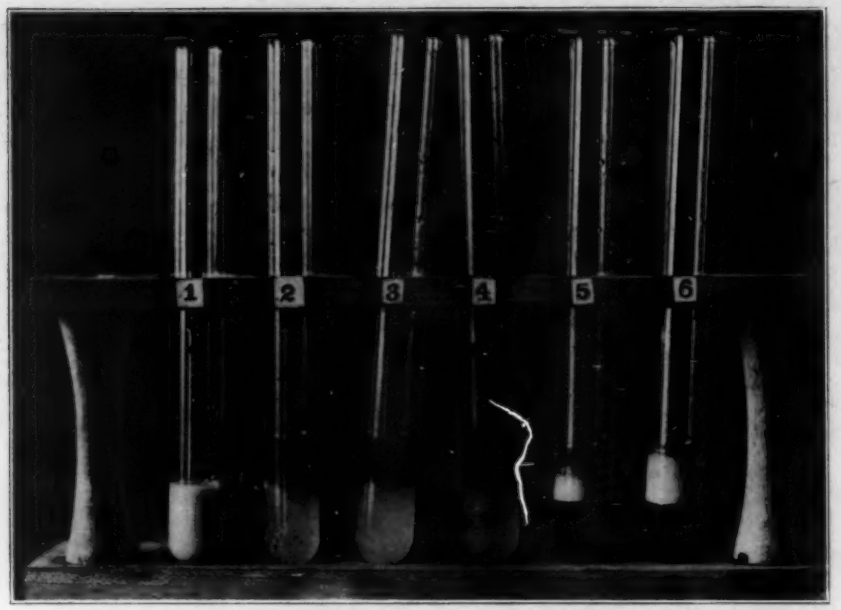


Fig. 8 (experiment 35).—Emulsion A, 5 cc., treated with reagents as follows: tube 1, none; tube 2, 3 cc. 1 per cent calcium lactate; tube 3, 3 cc. 0.2 per cent histamine; tube 4, 3 cc. 1 per cent peptone; tube 5, 3 cc. 0.5 per cent hemoglobin; tube 6, 3 cc. 1 per cent saponin. Calcium lactate, histamine and peptone show complete breakdown, hemoglobin and saponin partial breakdown; photographed at forty-eight hours.

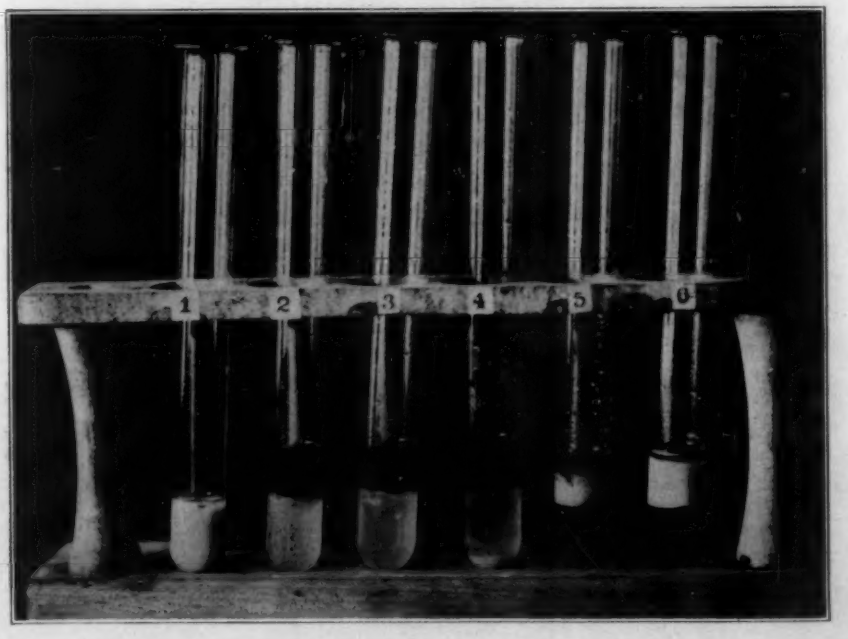


Fig. 9.—Same tubes as shown in figure 8 photographed at nine days to show permanence of the reaction.

The emulsion was treated on one occasion with the serum of a dog dead of experimental intestinal obstruction (fig. 5) and with the content of the obstructed loop. The result was a partial breakdown of the emulsion. This is recorded here only as a single observation which may confirm other analogous observations but on which, by itself, no weight should be put.

Other Substances: In one observation of pancreatin (commercial) and one of fresh pancreatic juice of the dog, there was complete breakdown of the emulsion (fig. 5).

Fresh Dog Bile: In two observations there was partial breakdown of the emulsion (fig. 6).

Sodium Taurocholate and Sodium Glycocholate (2 per cent solution): In one observation there was no breakdown of the emulsion (fig. 6).

Saponin: In three observations of a 1 per cent saponin solution, partial breakdown of the emulsion occurred twice (fig. 7).

Glucose: One observation was made with a 10 per cent solution of glucose prepared for intravenous medication. There was moderate breakdown of the emulsion.

### EMULSION B (FIG. 10)

Most of the foregoing reagents were tested repeatedly with the finer type of emulsion. The soap precipitants, hydrochloric acid and the various products of protein decomposition acted in a similar manner to emulsion A, except as noted below. Pancreatic juice, bile and bile salts were not employed. It was found that ether acts quite otherwise than with the coarse emulsion. The addition of ether immediately results in a gel resembling petroleum jelly, which is permanent on long standing in the test tube. If it is spread out on a flat surface, the ether rapidly evaporates, freeing the oil and water. If a large excess of ether is used, e. g., 20: 1, the gel is fine and flocculent and, in the course of a half-hour, disappears. Evaporation of the ether then leaves the oil and water in separate layers. If the ether is poured from the gel in the test tube and more ether is added, the oil fraction of the gel may promptly go into solution. In other words, the ultimate fate of the emulsion, when treated with ether with evaporation permitted, is destruction.

The striking difference in reaction between this emulsion and emulsion A is in the speed and completeness of the breakdown. Whereas the most active agent we studied, histamine, will destroy emulsion A in a few seconds, equal proportions will take several minutes to effect a change in emulsion B, and the freeing of the oil even after days is rarely complete. A layer of untouched emulsion lies between the watery layer below and the layer of oil above. This difference is well illustrated in figure 10, which was photographed ninety-six hours after the reagents

were added. There is, however, no question that necrotic muscle extract, peptone and histamine are all active in breaking down even so stable an emulsion as this.

The only difference in composition, to repeat, between emulsion A and emulsion B is in the fineness of the oil droplets. As we have said, on this fineness, among other things, hangs the stability of the emulsion. These findings, therefore, fit in with the theory of emulsions. More important for our purposes, however, they also help to explain the observations next to be detailed.

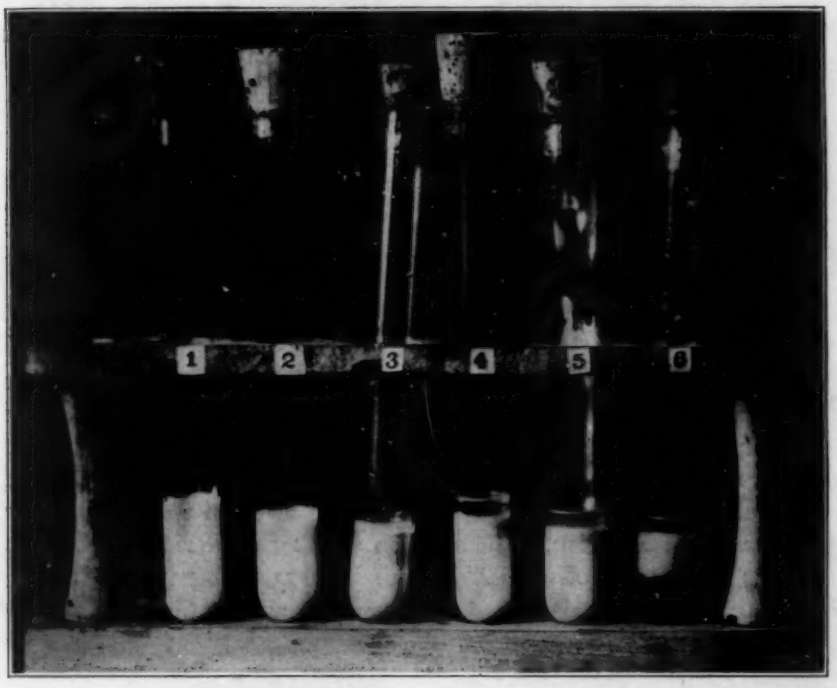


Fig. 10 (experiment 80).—Emulsion B, 5 cc., treated with reagents as follows: tube 1, 3 cc. of 0.7 per cent sodium chloride solution; tube 2, 3 cc. of saline extract of fresh muscle; tube 3, 3 cc. of saline extract of necrotic muscle; tube 4, 3 cc. of 0.2 per cent histamine solution; tube 5, 3 cc. of 1 per cent peptone solution; tube 6, 3 cc. of 2 per cent calcium lactate solution. Definite freeing of oil in tubes 4, 5 and 6; tube 3 showed a less degree of the same result although this is not obvious in the photograph; controls showed no breakdown of the emulsion; photographed at ninety-six hours.

### EMULSION C (FIG. 11)

Theoretically an ultramicroscopic emulsion of fat in blood serum might be expected to react in a manner similar to the reaction of the coarser artificial emulsions, provided only that proper alterations in proportions are made. Actually, with one exception as described below,

we were able to demonstrate no definite result with any of our reagents. On two occasions there was a doubtful freeing of fat following the addition of calcium lactate, and a similar doubtful change following the addition of a crystal of histamine.

Many reasons for this failure can be suggested. In the first place, technical difficulties are great. When the lipemic serum stands, the emulsion rises to the top within a few hours as a cream, which consists, at first, entirely of ultramicroscopic particles, the chylomicrons of Gage and Fish.[18] In the course of days, possibly from dessication, possibly

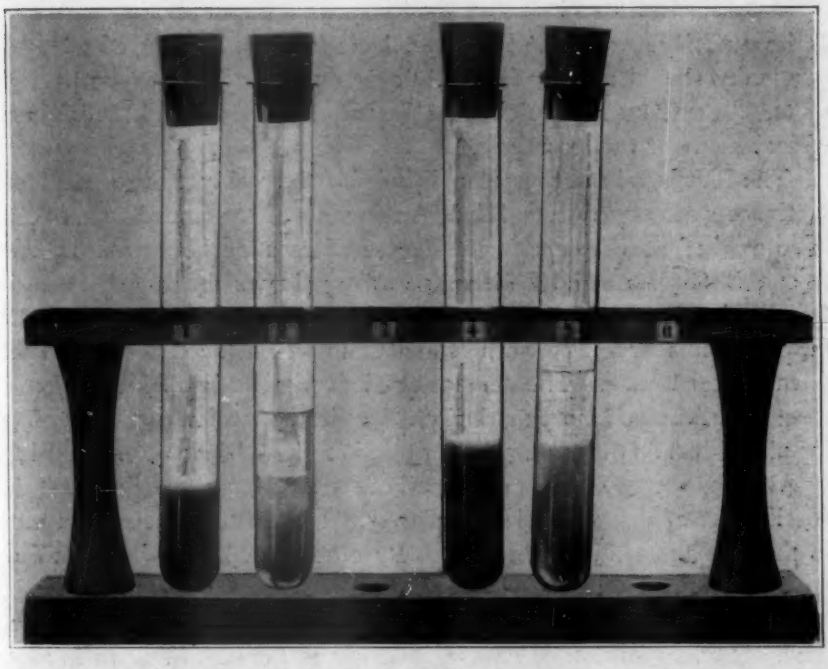

Fig. 11 (experiment 79).—Emulsion C (lipemic serum): this photograph was taken with a yellow screen and facing the light to show changes in transparency; the left tube of each pair shows the untreated emulsion; the right tube shows the emulsion treated with ether.

from putrefactive changes in the serum, possibly from other causes, free fat appears spontaneously. This, of course, confuses the reading of the experimental tubes. We have attempted to overcome this difficulty by using micro methods of reading within twenty-four hours of the experiment. Staining the cream for fat and observation under the darkfield microscope gave no added information. Attempts to demonstrate differences in the "greasiness" of the emulsion by allowing it to soak into paper were equally without result.

18. Gage and Fish (footnote 15, second reference).

A second possible reason for failure with emulsion C is in the enormous complexity of the external phase of the emulsion as contrasted with the simplicity of the external phase of the artificial emulsions. We are ignorant of what the effect of this difference may be on the stability of the emulsion. We attempted, however, to avoid the issue by washing the emulsion in physiologic sodium chloride solution through repeated dilution and centrifugalization. Apparently, the extreme agitation of the latter process acts much as the churn acts on cream. The emulsion agglomerated and could not again be dispersed.

A third reason lies in the possibility that some colloid other than soap is the emulsifying agent in this physiologic emulsion. Theoretically, this possibility should react unfavorably only on action by the soap precipitants. As we have said, calcium lactate may have had a slight breakdown effect on one or two occasions.

The fourth to be suggested and probably the real reason for the ineffectiveness of our reagents, lies in the fineness of the emulsion. If there is so marked a difference in the degree of reaction between emulsions A and B (figs. 6 and 10, histamine tubes), in which the difference in fineness is only moderate, then one can readily expect a much greater difference in reaction between B and C, in which the difference in the fineness is extreme. The surface tension relationships of emulsion C must demand much more marked changes in the tension of the enveloping phase than do the corresponding relationships of the coarser emulsion.

We do not feel that our experiments so far have exhausted the possibilities of demonstrating similar reactions in the plasma emulsion to those in the artificial emulsion. By other variations of the surface tension, of the $p_H$, of the viscosity of the blood serum, etc., it may be that the lipemic serum can be rendered sensitive to the reagents we have used. Such variations, of course, do occur in the blood stream in most conditions in which fat embolism occurs. These experiments will be undertaken as soon as opportunity arises.

We have noted one exception to the inertness of our reagents in experiments on emulsion C. That exception is the least interesting in regard to our fundamental argument, but has led to interesting in vivo results. The lipemic emulsion is immediately cleared with ether. This is well shown in figure 11, taken facing the light to show the transparency of the serum after treatment.

This observation is, of course, nothing new, but its application to the problem of fat embolism has led to the experimental production of fat embolism without trauma. The result will be described in the paragraphs detailing our in vivo experiments.

## SUMMARY OF IN VITRO EXPERIMENTS

1. Artificial soap-held emulsions of oil in water are destroyed, among other substances, by four classes of reagents, viz., (*a*) fat solvents, (*b*) soap precipitants, (*c*) acids and alkalis and (*d*) products of protein decomposition.

2. The rapidity and completeness of the effect varies with the fineness of the emulsified oil. The finer the emulsion, the less efficient is the reagent.

3. The physiologic emulsion of fat in blood serum seems to be destroyed only by the fat solvents.

4. On a theoretical basis no good reason for this difference can be adduced, except the greater fineness of the lipemic emulsion. Experiments on points 3 and 4 are not yet complete.

## IN VIVO EXPERIMENTS

Recapitulation of the results of study of the literature and of our test tube experiments leads to three important conclusions, viz., 1. Not all fat embolism is of traumatic origin. 2. The normal emulsion of fat in the blood stream is a possible source of fat in nontraumatic fat embolism. 3. The action of certain substances which are present in the blood stream in pathologic states offers, on the basis of experiments with artificial emulsions, a possible mechanism for the freeing of this fat from the emulsified state. Attempts to demonstrate the operation of this mechanism in the blood serum in vitro have not succeeded.

Attempts to produce nontraumatic fat embolism in vivo may be divided into two groups. In the first of these, calcium lactate and histamine, substances not definitely effective in vitro, were employed. In the second we made use of ether, which gave positive results in the test tube.

Before we detail these experiments, it is important to define technical procedures and standards on which estimation of the results depends. An experience covering the examination of over 250 microscopic sections for fat has shown us that decision on the presence or absence of fat embolism is not always easy. Certain pitfalls into which many observers have undoubtedly fallen are mentioned by some experimenters, particularly Caldwell and Huber.[19]

The problem of staining on which many authors lay stress has not offered difficulties to us. Throughout we have used sudan III in the form of a saturated solution in 70 per cent alcohol. In every section examined, normal fat in the tissue such as that described below, took the stain clearly and thereby automatically controlled the staining of pathologic fat.

19. Caldwell and Huber (footnote 4, sixth reference).

Tissue was placed in formaldehyde immediately on the death of the animal. At the end of twenty-four hours or more of hardening, it was cut by the freezing microtome, stained with sudan III, and mounted in glycerine. In removing lungs for hardening, we made comparisons in many animals between one lung from which the blood was allowed to drain and the other of which the hilum was ligated before division. In the same animal no difference between the amounts of fat in the two lungs thus treated could be detected. In later experiments, therefore, no ligation was done.

All observers agree that in any type of fat embolism, even when experimentally produced by the arterial injection of an extremity, most of the fat is found in the lungs. This is usually explained on the basis of the lower arterial pressure and the greater distensibility of the capillaries here. Whatever the cause, the lungs furnish the most useful index for the presence of fat embolism. Although kidneys, medulla and liver were preserved from most experimental animals, the conclusions of this portion of our studies are based largely on the lung findings.

Sudan III demonstrates normal fat in the lung of the dog in three different sites: 1. About the large bronchi there are often found a few cells of normal adipose tissue. 2. In the epithelial cells of the bronchial mucosa and in some animals even of the mucosa of the finer bronchioles are found droplets of fat. In cross sections of the bronchus these are not confusing, but in tangential section they may mislead the observer. 3. Finally, throughout the capillaries of the lung, most profuse in the periphery directly under the pleura, many leukocytes are found, even in dogs starved for twenty-four hours, that show ingested fat globules varying in diameter from just visible points to 3 or 4 microns. These are usually easily recognized if the observer is alert for them.

However, we have found that any or all of these normal deposits of fat may falsify results in a manner not mentioned by any previous experimenter. If the tissue is not completely frozen, the microtome knife can pick up fat droplets in passing and spread them through the section. This danger became obvious to us on one occasion when sections from the same block of tissue cut with a failing tank of carbon dioxide and with a fresh tank showed, in the first instance, what might easily pass for fat embolism and, in the second instance, nothing but the normal fat. With this experience to warn us, we took pains to insure complete solidification of the entire tissue, including the fat, before cutting.

A source of error that we controlled in many observations was the accidental presence of fat on the slides on which the sections were stained. These were frequently washed with ether before staining. We feel, however, that this is an unnecessary refinement for two reasons. In the first place, many exudates and a large proportion of the controls,

were stained on unprepared glassware with negative results. In the second place, our criteria for positive results as outlined in the next paragraphs automatically rule out accidental droplets.

With these sources of possible error in mind, the interpretation of stained fat not in the three sites mentioned is often difficult. To guide us in deciding whether or not fat droplets seen in lung sections were embolic fat, we took into consideration in every instance (1) the amount of free fat seen; (2) its distribution in sections taken from different areas of both lungs; (3) its distribution in any one section in relation to bronchi, and (4) its unequivocal presence in capillaries.

No lung was considered to present evidence of fat embolism on the basis of one or two fat droplets to a section. The sources of error described could easily account for that amount. In addition no measurement of the amount of trauma that will liberate fat has been or can easily be made. All the dogs were subjected to trauma, if one includes in that term the amount of constraint necessary to control a dog struggling under an anesthetic. Such slight mechanical disturbance might account for minimal freeing of fat from the depots. A profuse amount of fat was usually unequivocal. In between these two grades there were a few animals in which the other criteria governed.

A diagnosis of fat embolism was made only if fat droplets were found in almost all fields in at least three sections from different areas of the two lungs. The distribution of emboli, even in the experimental injection of fat, is irregular. Some sections will be rich in fat, others will show little or none. For that reason one or two negative sections do not invalidate three or more positive sections. In the same sense, negative fields in an otherwise positive section are not of importance. The more sparse the fat, the more thoroughly we insist on wide distribution before diagnosing embolism.

In certain sections, the fat observed was found to be in fairly close relation to large bronchi. This fat was ignored in making the diagnosis. There was a possibility that it might have been spread by the microtome knife, or that it might be in the mucosa of a branch bronchus approaching the main stem and cut tangentially. Particularly in the fat fed dogs it might represent intragastric fat, vomited and aspirated. In one animal this had undoubtedly occurred.

Finally, no diagnosis of fat embolism was made unless the section showed definitely that some of the fat was in the capillaries. It need not all be in the capillaries, as embolic fat rapidly passes into the alveoli. Warthin [1] made use of this fact in diagnosing fat embolism clinically from the presence of fat in the sputum.

The absence of fat embolism as exemplified by control experiments will be taken up when they are discussed.

### CALCIUM LACTATE AND HISTAMINE INJECTION

Although neither calcium lactate nor histamine gave definitely positive results in destroying serum emulsions in the test tube, it was considered possible that under physiologic conditions in the blood stream, the effect observed in treatment of artificial emulsions by these reagents might be obtained. Attempts were therefore made to bathe the blood stream for a considerable period in one or the other of these substances. In order to intensify possible effects, a digestive lipemia was established. Dogs were weighed and fed from 1 to one-half pint (473.1 to 236.5 cc.) of cream. At the same time they were given 0.1 Gm. of amythal per kilogram (isoamyl ethyl barbituric acid) administered by stomach tube. Once the same dose was given by intramuscular injection somewhat later. One experiment was done under local anesthesia alone. From two to four hours after feeding, the jugular vein was exposed and a cannula inserted. Through the cannula the solution was run under gravity in small amounts at brief intervals. Injection was continued until death occurred or until at least two hours had elapsed.

There is no need to report these experiments in further detail. Three experiments were done with calcium lactate and three with histamine. In none of the six did frank unmistakable embolism occur. This group of studies was not pursued further, as our attention was diverted by the striking results obtained with ether. However, as is the case with the corresponding test tube investigations, the experiments cited are not considered exhaustive. The conditions of the experiments must be varied greatly and many more repetitions must be made before we can pronounce them completely negative. In addition, experiments with peptone, necrotic muscle extract, bile and pancreatic juice must be carried out. All these procedures are contemplated for the immediate future.

The dogs in this series that show no free fat whatever in the lungs appear among the controls for the next series of experiments (table 4).

### ETHER ADMINISTRATION

Two types of experiments were performed, namely, administration of ether (1) intravenously and (2) by inhalation. A discussion of the controls will follow the description of these experiments.

*Intravenous Ether (Tables 1 and 2).*—Seven dogs were given varying quantities of ether intravenously after a fat meal, and four starved dogs were similarly treated. The tables furnish most of the details of the experiments and their results.

Columns 1 to 4 inclusive in table 1 are self explanatory. Column 5 (chylomicron estimate of lipemia) records our check on the digestion and absorption of fat. As cited by Leathes and Raper,[16] Terroine

TABLE 1.—*Results of Intravenous Ether Anesthesia in Fat Fed Dogs*

| Dog | Weight Dog Kilograms | Amount of Cream Fed | Interval Between Fat Feeding and Beginning of Anesthesia | Chylomicron Estimate of Lipemia | Duration of Anesthesia | Quantity of Ether Administered | Amount of Vomiting | Amount of Artificial Respiration | Amount of Trauma | Amount of Pulmonary Edema | Amount of Fat Embolism |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 17 | 7 | ½ pint | 1 hour, 30 minutes | Moderate | 1 hour, 30 minutes | 11 cc. | None | 1 minute | Slight | Fatal | A few emboli |
| 18 | 8 | ½ pint | 1 hour, 15 minutes | Moderate | 34 minutes | 7.5 cc. | None | 3 minutes | Slight | Fatal | Many emboli |
| 20 | 6 | ½ pint | 1 hour, 40 minutes | Light | 11 minutes | 8 cc. | None | None | Very slight | Moderate | A few emboli |
| 21 | 7 | ½ pint | 1 hour, 30 minutes | Moderate | 32 minutes | 10 cc. | None | None | Very slight | Fatal | Many emboli |
| 22 | 7 | ½ pint | 1 hour, 15 minutes | ..... | 42 minutes | 9 cc. | None | None | Very slight | Fatal | Many emboli |
| 40 | 7 5 | ½ pint | 1 hour, 20 minutes | ..... | 1 hour, 30 minutes | 13.5 cc. | None | 2 minutes | Slight | Fatal | Many emboli |
| 42 | 8 | ¼ pint | 2 hours, 30 minutes | Moderate | 1 hour, 10 minutes | 6 cc. | None | None | Very slight | Fatal | Many emboli |

TABLE 3.—*Results of Inhalation Ether Anesthesia in Fat Fed Dogs*

| Dog | Weight Dog Kilograms | Amount of Cream Fed | Interval Between Fat Feeding and Beginning of Anesthesia | Chylomicron Estimate of Lipemia | Duration of Anesthesia | Quantity of Ether Administered | Amount of Vomiting | Amount of Artificial Respiration | Amount of Trauma | Amount of Pulmonary Edema | Amount of Fat Embolism |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 46 | 12 | ½ pint | 1 hour | Moderate | 6½ hours | 1,000 cc. | None | None | Very slight | Slight | Very many emboli |
| 47 | 6 | ½ pint | 2 hours | Heavy | 5½ hours | 660 cc. | None | None | Very slight | None | Many emboli |
| 48 | 8 | ½ pint | 1 hour, 15 minutes | Very heavy | 6¾ hours | 400 cc. | None | None | Very slight | Slight | Many emboli |
| 49 | 7 | ½ pint | 1 hour, 20 minutes | Heavy | 6⅔ hours | 500 cc. | Considerable | 3 minutes | Moderate | Moderate | A few emboli |
| 50 | 11 | ½ pint | 1 hour, 30 minutes | Heavy | 6½ hours | 400 cc. | None | 3 minutes | Slight | Moderate | A few emboli |
| 51 | 5 | ½ pint | 2 hours | Heavy | ¼ hour | 30 cc. | None | None | Moderate | None | Many emboli |
| 52 | 11 | ½ pint | 2 hours | Very heavy | 5¾ hours | 500 cc. | None | 5 minutes | Slight | Marked | Very many emboli |
| 53 | 9 | ½ pint | 2 hours | Very heavy | 4⅞ hours | 400 cc. | None | None | Very slight | Marked | Very many emboli |
| 54 | 7 | ½ pint | 2 hours | Moderate | 5¾ hours | 500 cc. | None | 6 minutes | Slight | Slight | Many emboli |

observed differences in degree of lipemia in different dogs under similar conditions. We have in most instances made a rough estimate of the degree of lipemia following the fat meal by observing the richness of the blood in dancing particles under the dark field microscope. Columns 6 and 7 need no comment. Columns 8, 9 and 10 control the factor of possible traumatic embolism. We have remarked that concussion without fracture can produce fat embolism. We have considered it possible that the struggling of early anesthesia, retching and sharp pressure on thorax and abdomen (as in artificial respiration) might conceivably have similar effects. The amount of trauma (column 10) is recorded as "very slight" when only the struggling, attendant on induction of anesthesia, occurred, and as "slight" when either of the other two factors was present. Incision into fat tissue in the neck to expose the jugular vein is a constant concomitant of these experiments and adds a minute traumatic element. The occurrence of vomiting (column 8) is a check

TABLE 2.—*Results of Intravenous Ether Anesthesia in Dogs Starved Twenty-Four Hours*

| Dog | Weight of Dog in Kg. | Chylomicron Estimate of Lipemia | Duration of Anesthesia | Quantity of Ether Administered | Amount of Vomiting | Amount of Artificial Respiration | Amount of Trauma | Amount of Pulmonary Edema | Amount of Fat Embolism |
|---|---|---|---|---|---|---|---|---|---|
| 23 | 6 | Extremely light | 43 minutes | 7 cc. | None | None | Very slight | Slight | Very few emboli |
| 24 | 13 | Extremely light | 50 minutes | 23 cc. | None | None | Very slight | Fatal | No emboli |
| 25 | 5 | Extremely light | 39 minutes | 6 cc. | None | None | Very slight | Fatal | A few emboli |
| 41 | 8 | Extremely light | 18 minutes | 5 cc. | None | 5 minutes | Slight | Slight | Many emboli |

also on the possibility that fat found in the lungs might have been aspirated. Column 11 (amount of pulmonary edema) records an interesting finding. Eight of the eleven dogs died unquestionably from pulmonary edema and in the remaining three dogs pulmonary edema was definitely present. This effect of intravenous ether is in striking contrast to the effects observed in the dogs given prolonged inhalation anesthesia (table 3). In none of the latter was the edema fatal. In the intravenous experiments, frothy pink fluid to the amount of 100 cc. or more poured from the nose and mouth. This pulmonary edema is not to be confused with that frequently described as associated with fat embolism. It is purely toxic in origin. The reason for this assertion is that the degree of fat embolism produced in these dogs did not even approach that which can be caused by intravenous injection of oil without the production of edema. Column 12 can best be understood by referring to the paragraphs above on the criteria for diagnosis of fat embolism.

When we survey this table, judgment must be reserved on the possible sources of error until the discussion of controls (table 4) has been read.

Table 2 needs no comment other than that given for the corresponding columns above in table 1.

A sample protocol follows:

PROTOCOL

EXPERIMENT 75.—Dog 42; March 31, 1926; weight, 8 Kg.

| | |
|---|---|
| 11:00 a. m. | Given one-half pint (236.5 cc.) of thin cream; drank it promptly. |
| 2:00 p. m. | Ether anesthesia; femoral vein exposed. |
| 2:05 | Moderate number of chylomicrons in dark field examination of blood. |
| 2:06 | Mask ether stopped; intravenous ether, 0.5 cc. |
| 2:10 | Ether intravenously, 0.5 cc. |
| 2:12 | Ether intravenously, 0.5 cc. |
| 2:15 | Ether intravenously, 0.5 cc. |
| 2:16 | Ether intravenously, 0.5 cc. |
| 2:18 | Ether intravenously, 0.5 cc. |
| 2:20 | Ether intravenously, 0.5 cc. |
| 2:22 | Ether intravenously, 0.5 cc. |
| 2:26 | Ether intravenously, 0.5 cc. |
| 2:28 | Ether intravenously, 0.5 cc. |
| 2:40 | Ether intravenously, 0.5 cc. |
| 2:53 | Ether intravenously, 0.5 cc. |
| 3:10 | The dog died suddenly. On suspending it by the hind legs, frothy pink fluid ran from the mouth. This showed fat globules on staining with sudan III. However, it was contaminated by buccal content. |

Necropsy: The lungs showed typical changes of pulmonary edema, most marked at the bases; they were removed without ligation of the hilum.

Microscopic examination with sudan III revealed many fat emboli.

These experiments have demonstrated to our satisfaction that fat embolism can be produced experimentally by the intravenous injection of ether. We believe the mechanism to be that of the test tube. The ether in the blood stream takes into solution the circulating emulsified droplets. As the ether vapor passes into the alveoli, the ether vapor tension in the blood is lowered to a point at which the fat comes out of solution as free fat. The emulsifying power of the blood is not sufficient, particularly in the slowly moving capillary bed of the lung, to reform the original fine emulsion. Fat emboli visible under the ordinary microscope thus appear.

It may be asked whence in the starved dogs enough fat can accumulate to produce any embolism. The degree of embolism in the starved dogs is seen, on the average, to be much less than in the fat fed dogs (tables 1 and 2). A possible explanation for embolism in the starved dog may be found by comparing the results of Bloor's chemical analyses of the blood under ether anesthesia,[20] with the results of chylomicron observations by Day [21] and by Schroeder and Holt.[22] The latter two

20. Leathes and Raper (footnote 16, p. 162).

21. Day, M. G.: Am. J. Surg. **36**:53 (April) 1922, cited by Schroeder, L. C., and Holt, E.: Chylomicron (Free Fat) Content of Blood in Infants, Am. J. Dis. Child. **31**:201 (Feb.) 1926.

22. Schroeder and Holt (footnote 21).

studies report a diminution of chylomicron counts during ether anesthesia. This finding has been confirmed by us in the next series of experiments to be reported. Bloor, on the contrary, found a rise of as much as 50 per cent in the blood fat during ether administration using chemical methods. These two findings, considered contradictory by Schroeder and Holt, are really not so. The diminution in chylomicron count does not mean diminution in blood fat. The physical state of the fat is simply altered so that it is no longer visible as chylomicrons. A diminution of chylomicron count can proceed simultaneously with an increase in total blood fat, and to accept Bloor's results, probably does. This increase in

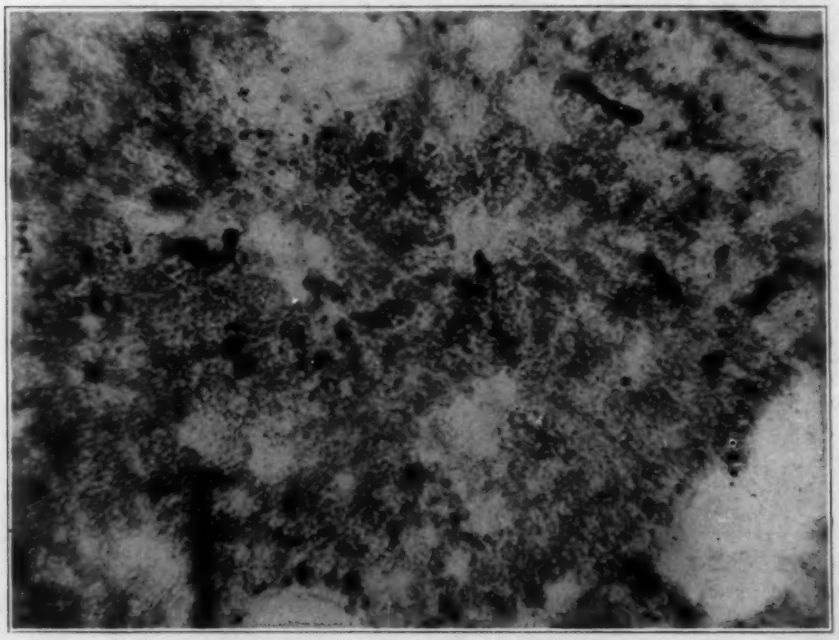

Fig. 12.—Lung of dog 18 after intravenous ether, under low power (sudan III).

fat may be due to the solution of depot fat by the ether vapor circulating with the blood. If fat is so dissolved, then its relation to the lowering of the ether vapor tension in the blood is exactly the same as that of the dissolved chylomicron fat. That is, fat emboli would result. In other words, somewhat less fat is available in the starved dogs than in the fat fed dogs; but enough fat can be taken up by the circulating ether vapor to create embolism.

Examination of these lungs stained with sudan III (figs. 12 and 13) shows not only the ordinary drops that fill capillaries but also a type of much finer droplet from about 2 to 7 microns in diameter. These are

found richly scattered in capillaries, and can be observed only by the higher power lenses. A few such droplets can be made out in figure 13. They are interpreted as an intermediate stage in the agglomeration of fat. They can therefore be regarded as presenting evidence confirmatory of our conception of the mechanism of production of fat embolism by ether administration.

We emphasize at this point one fact, namely, fat embolism has been produced by intravenous ether administration, whatever weight one may care to place on the theoretical considerations discussed.

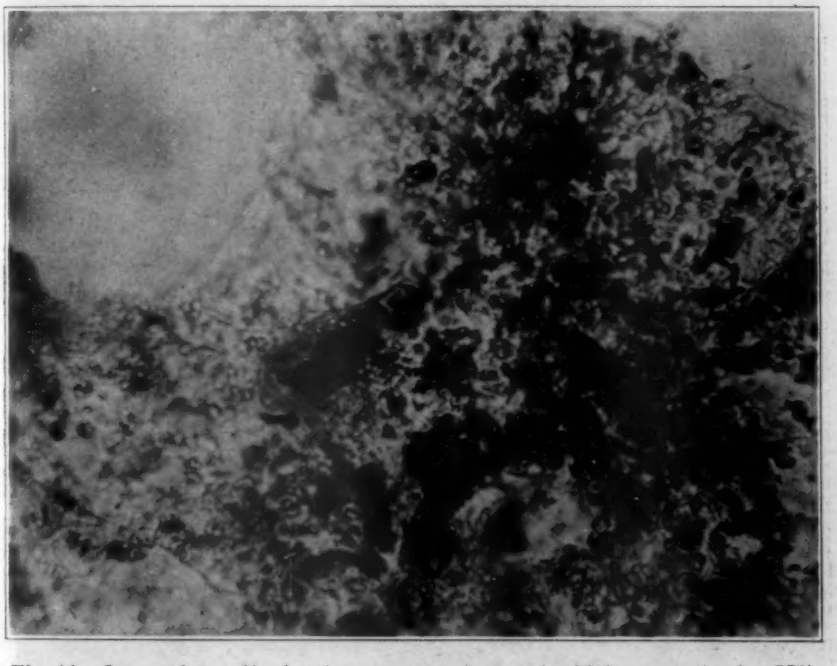

Fig. 13.—Lung of dog 40 after intravenous ether, under high power (sudan III).

*Ether by Inhalation* (table 3).—The technic of these experiments is of the simplest order. Nine observations were made. In all of these, conditions were rendered favorable for ether action by creating a digestive lipemia. Table 3 records the varying conditions of the nine experiments. The column headings need no explanation further than that given for table 1.

A sample protocol follows:

PROTOCOL

EXPERIMENT 84.—Dog 47; April 10, 1926; weight, 6 Kg.

10:00 a. m. Given one-half pint (236.5 cc.) of cream by stomach tube.
12:00 m. Ether anesthesia begun; no retching or violent struggling.
12:30 p. m. Heavy grade lipemia. (This, and corresponding observations below, refer only to chylomicron estimates under the dark field microscope.)
1:45 Still heavy lipemia.
2:45 Moderately heavy lipemia.
5:10 Moderate lipemia.
5:30 Anesthesia crowded to fatal termination.
Total: 5½ hours; 21-22 ounces (621-650 cc.) of ether.

Fig. 14.—Lung of dog 47 after inhalation ether, under high power (sudan III).

Throughout the entire period of the anesthetic there was no dyspnea, no increase in respiratory effort and no vomiting or retching. The dog's tongue was kept forward with a hemostat. The corneal reflex was present at all times. Early in the experiment a 2 cm. linear incision was made through the skin in the inguinal region and a blood drop was secured for estimate of lipemia by cutting a minute subcutaneous vessel. No appreciable loss of blood occurred. There was no disturbance of any fat depot.

The lungs were removed without ligation of the hilum and placed in formaldehyde.

Microscopic examination with sudan III showed areas of embolic fat (figs. 14 and 15).

Fig. 15.—Lung of dog 47 after inhalation ether, under high power (sudan III).

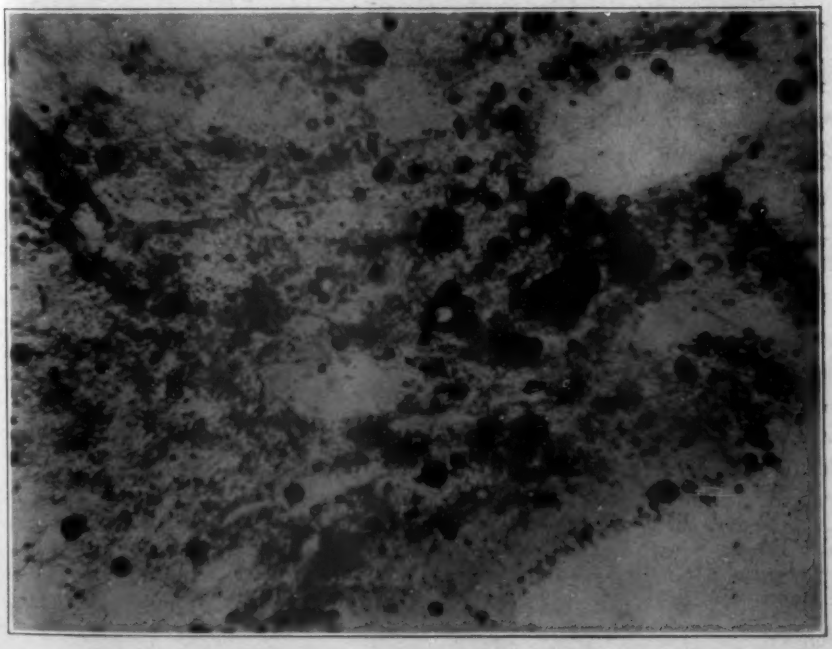

Fig. 16.—Lung of dog 46 after inhalation ether, under low power (sudan III).

These experiments confirm the finding that ether vapor in the blood stream will produce fat embolism, at least in the presence of digestive lipemia. They further show that the introduction of ether by inhalation is possibly more effective than by intravenous injection. Dog 46 (figs. 16 and 17) showed throughout both lungs at least as great a degree of embolism as we have produced with the intravenous injection of pure olive oil in amounts of 1 cc. per kilogram, and dog 52 showed almost as much. Both of these were far greater than anything seen with intravenous ether. Figures 18 and 19 show lung fields from two other dogs of this series. Figure 19 from the lung of dog 50 illustrates what is meant by the description in table 3—"a few emboli."

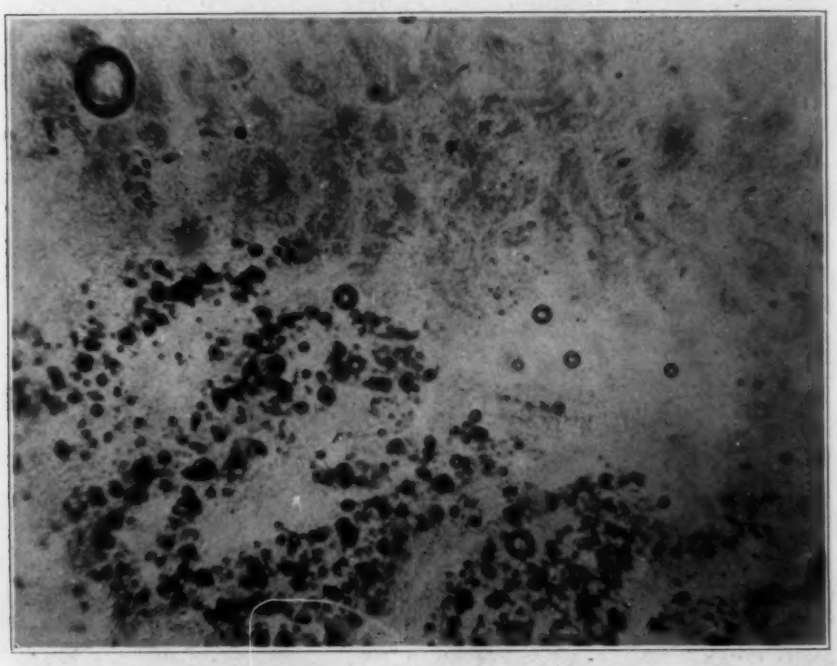

Fig. 17.—Kidney of dog 46 after inhalation ether, under low power (sudan III).

The reason for the difference between the results in the intravenous and in the inhalation methods of administration is probably the fact that in the former the blood stream was bathed in ether for a shorter period than in the latter. The toxic effect of intravenous ether on the lung rapidly produces a pulmonary edema that cuts short the experiment at a relatively brief period by killing the animal.

One experiment (dog 51) was done with a short ether anesthesia of fifteen minutes. An interesting finding here, in addition to the occurrence of embolism, was that the embolic fat was on the average in a much finer state of division than in any other dog of this series. In other words, the process of agglomeration had not had time to progress far.

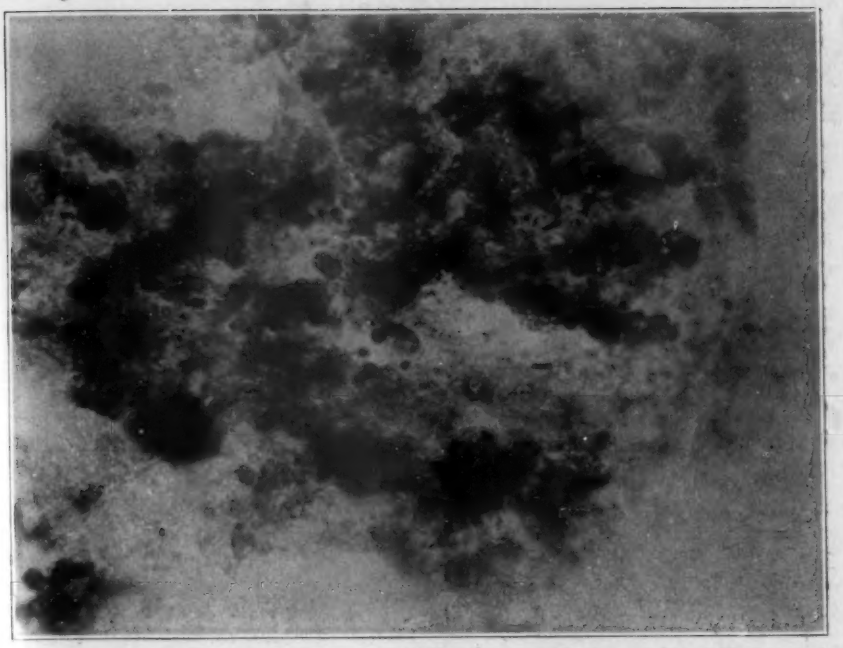

Fig. 18.—Lung of dog 48 after inhalation ether, under high power (sudan III).

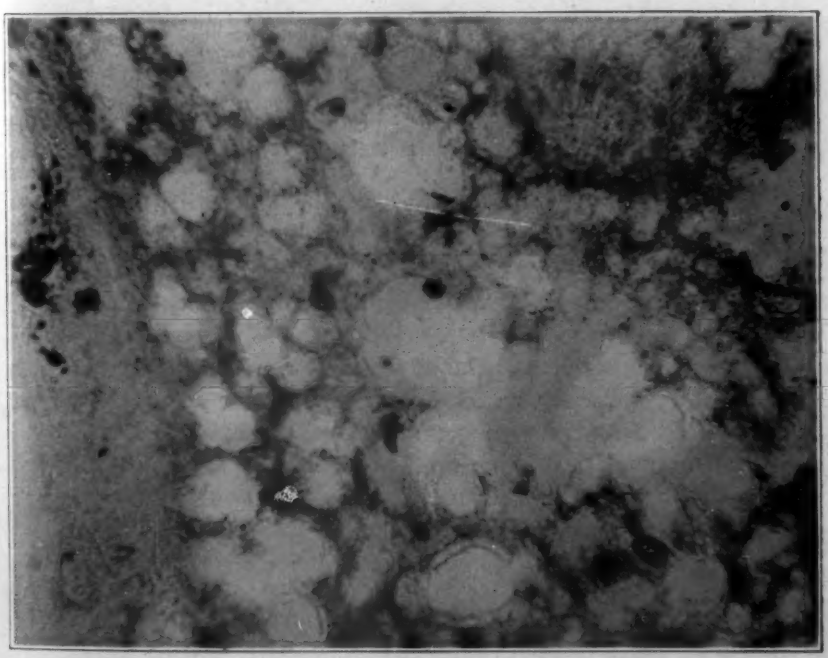

Fig. 19.—Lung of dog 50 after inhalation ether, under low power (sudan III).

Five of the nine dogs in this series had repeated estimations of chylomicrons in the blood throughout the course of the anesthesia. In all there was a gradually diminishing number.

What has been said as to the probable mechanism of the appearance of emboli following intravenous injection of ether will hold in regard to the inhalation experiments. The method of introduction of the ether into the blood stream is immaterial.

*Controls* (table 4).—The presence of fat embolism in the experimental dogs is for the most part unmistakable. Certain of them, however, showed minimal degrees. What degree of trauma will cause a minimal degree of fat embolism is not known. What alterations in chemical and physical characteristics of the blood will do the same is equally unknown. That normal blood with moderate fat content shows

TABLE 4.—*Control Dogs*

| Dog | Weight in Kilograms | Amount of Cream Fed | Chylomicron Estimate of Lipemia | Anesthesia Used | Mode of Death | Amount of Trauma | Amount of Fat Embolism |
|---|---|---|---|---|---|---|---|
| 1 | 10 | None | Not done | Ether 20 hours before death | High intestinal obstruction | Moderate | No emboli |
| 9 | 3.3 | None | Not done | 0.3 Gm. Barbituric acid derivative | Histamine intravenously | Slight | No emboli |
| 10 | 10 | None | Not done | 1 Gm. Barbituric acid derivative | Bled to death | Slight | No emboli |
| 11 | 6 | ¾ pint | Not done | Local | Bled to death | Slight | No emboli |
| 7 | 10 | 1 pint | Not done | Local | Bled to death | Slight | No emboli |
| 6 | 8 | ¾ pint | Not done | 0.8 Gm. Barbituric acid derivative | Bled to death | Slight | No emboli |
| 2 | 10 | 1 pint | Not done | 1 Gm. Barbituric acid derivative | Calcium lactate intravenously | Slight | No emboli |
| 3 | 10.5 | 1 pint | Not done | 1 Gm. Barbituric acid derivative | Histamine intravenously | Slight | No emboli |
| 4 | 10 | 1 pint | Not done | 1 Gm. Barbituric acid derivative | Bled to death | Slight | A few emboli |
| 5 | 10 | 1 pint | Not done | 1 Gm. Barbituric acid derivative | Bled to death | Slight | A few emboli |
| 43 | 8 | ½ pint | Heavy | Local | Bled to death | Slight | No emboli |
| 55 | 8 | ½ pint | Light | None | Sodium cyanide | Slight | Many emboli |
| 56 | 8 | ½ pint | Heavy | None | Sodium cyanide | Slight | No emboli |
| 57 | 6 | ½ pint | Very heavy | None | Sodium cyanide | Moderate | No emboli |

no free stainable fat is certain. Whether the same is true of blood with a rich digestive lipemia is a question that must be answered. It is impossible to cause the death of an animal without both trauma, even if slight in amount, and chemical alteration of the blood. In the lipemic plasma, the effect of the latter in causing embolism will be magnified. Each dog in the experimental series, therefore, represents a complex of different possible causes of fat embolism. The dogs showing relatively slight embolism need the strictest controls.

On account of the probably multiple factors that may cause fat embolism, a series of control animals need not show absolute freedom from this finding. It will suffice to establish the validity of the experiments if dogs given ether show a decidedly higher embolic rate than do dogs killed in all other ways.

Table 4 represents the control dogs. Seven dogs were bled to death under cocaine, used locally, or a barbituric acid derivative. Of these six were fat fed. Two of the latter showed a few emboli. As a check on the possibility that in these seven dogs fat emboli were washed out by the excessive hemorrhage that caused death, two facts can be mentioned. In the first place, in the lung capillaries of all these dogs the usual number of fat containing leukocytes could be made out. In the second place active bleeding from the carotid should have less effect in emptying the lung capillaries than passive bleeding from the pulmonary veins of the excised lung. This, we have seen, does not remove emboli. The presence of emboli in two of this series is additional evidence.

Three fat fed dogs were killed instantaneously by intracardiac injections of 20 per cent sodium cyanide solution. One dog showed many emboli; the other two showed none.

TABLE 5.—*Recapitulation*

| | Ether Experiments | | Controls | |
|---|---|---|---|---|
| | Embolism | No Embolism | Embolism | No Embolism |
| | Fat Fed | | Fat Fed | |
| | 16 | 0 | 3 | 8 |
| | Not Fat Fed | | Not Fat Fed | |
| | 3 | 1 | 0 | 3 |
| Totals | 19 | 1 | 3 | 11 |
| | Percentage of Embolism = 95 | | Percentage of Embolism = 21 | |

Three dogs are included from the calcium lactate and histamine experiments as they represent other causes of death. One of these was killed by histamine without previous digestive lipemia, and one following a fat meal. The third is a fat fed dog killed by prolonged calcium lactate injection. None of these three showed fat embolism. (The choice of three negative animals from a series of six for use as controls, needs no explanation. The other three dogs showed questionable embolism. This finding, in this particular series, may be the result of the injection of histamine or of calcium lactate on the basis of our *a priori* reasoning. These three dogs, therefore, are useless as controls.)

One dog that had had ether anesthesia for thirty minutes the previous day for the experimental establishment of intestinal obstruction and that had died of this condition in twenty hours is included. This dog, of course, was not fat fed. No embolism occurred.

Table 5 recapitulates these controls and compares them with the consolidated experimental results. The markedly higher embolic rate in the entire series of ether dogs over the control dogs is conclusive. Ninety-five per cent of the former showed fat embolism as compared with 21 per cent of the latter.

GENERAL CONCLUSIONS OF PART I

To put the results of this study in general terms, we have shown that the blood fat (and possibly also the nontraumatized depot fat) is a source of fat in fat embolism, and we have demonstrated one means by which the blood fat can be made to become embolic; namely, by the administration of ether. We have further presented evidence suggesting other mechanisms by which the same result might be expected to be brought about, mechanisms that undoubtedly are available in the body in many cases of fat embolism; namely, the action of products of protein decomposition. We have indicated the path of future experimentation to prove or disprove the actual causation of fat embolism by this means.

The significance of these findings is both theoretical and practical. Three practical considerations may be presented.

1. *Fat Embolism and Ether Anesthesia in Clinical Surgery.*—It is not at all improbable that certain ether deaths after prolonged anesthesia may have been caused by fat embolism, by exactly the mechanism we have demonstrated. That more such deaths have not occurred may be due to the general practice of starvation before ether anesthesia, a starvation that has been imposed for other reasons. It is possible, also, that a proportion of postoperative pulmonary complications, usually ascribed to thrombotic emboli, may actually be the result of fat emboli in the lungs. Certainly, these possibilities are suggestive enough to offer another sound reason for starvation previous to ether anesthesia.

2. *Fat Embolism and Intravenous Medication.*—The literature of fat embolism in poisonings and the results of our test tube experiments strongly suggest that the physical state of the blood fat should receive consideration in every instance in which medicaments are introduced into the blood stream. Certainly, the effect of such treatment of the blood on the physical state of the blood fat has received no consideration. Even in such exhaustive studies as that of Hanzlik and his co-workers,[23] who observed many physical and chemical changes in the blood after scores of different agents were introduced intravenously, no mention is made of the possibility of any change in the plasma emulsion, much less of any symptoms arising therefrom. It is conceivable that certain injection reactions may be induced by this mechanism. One would do well, until this point is proved or disproved, to inject no untried substance except when the plasma fat content is minimal.

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23. Hanzlik, P. J., and Karsner, H. T.: J. Pharm. & Exper. Therap. **23**:173 (April) 1924. Hanzlik, P. J.; De Eds, F., and Tainter, M. L.: Blood and Symptomatic Changes Following Intravenous Administration of a Variety of Agents and Solutions, Arch. Int. Med. **36**:447 (Oct.) 1925.

3. *Fat Embolism and Shock.*—We have proved nothing in regard to fat embolism and the products of tissue disintegration. Theoretically, however, the possibility that fat embolism may intervene in the course of delayed shock, on the basis of experiments here presented, seems strong. It seems at least sufficiently strong to warrant the recommendation that no patient suffering from shock or showing symptoms from absorption of products of protein breakdown, should be given a diet of high fat content. Particularly is this true of burns, in which fat embolism has often been demonstrated.

The results of our experimentation seem to us of the greatest theoretical importance. The physical state of the fat in the blood has not received consideration from pathologists or pathologic physiologists. It seems to have fallen on a universally distributed blind spot. That this physical state has any pathologic significance has not only received no consideration but, as we have noted, has actually been denied. Our experiments represent the first proof, so far as we have been able to determine, that changes in the physical state of blood fat may have pathologic significance.

## PART II. EFFECTS OF FAT EMBOLISM

The pathogenesis of fat embolism is not the only aspect of this condition that is obscure. The effects of fat embolism, as expressed in clinical and pathologic changes, are often equally unexplained. Contradictory observations abound. There is no constant relationship between the amount of fat found at necropsy and the amount of fat disturbed by trauma. Parenthetically, it may be repeated that the results recorded in Part I may possibly be found sufficient to explain this discrepancy. Further there is no constant relationship between the amount of fat found at necropsy and the severity of symptoms. For the latter discrepancy there has never been offered even a working explanation, such as that suggested for the former. To reach an explanation, prolonged study of the quantity of embolic fat, its distribution under differing circumstances and its physical and chemical characteristics will be required. In this portion of this article we will attempt to clear the field for such a study by summarizing what evidence has already been presented. In addition, we will report a few of our tentative experiments attacking the problem, experiments that serve only to throw into bolder relief the essence of the contradictions involved.

We are not pioneers in this phase of the problem. By far the greatest amount of experimental work on fat embolism has been done by the intravascular injection of oils and the study of their effects and their fate.

Magendie (1827) was the first to recognize that fluid fat might obstruct the blood vessels. Virchow (1865) injected oil into a neck

vein of a dog and produced fatal fat embolism which was accompanied by acute pulmonary edema. Scriba (1879),[24] after experimental observations, pointed out that a drop of fat could pass through the lungs without difficulty; previously a patent foramen ovale had been considered essential to the passage of embolic fat from the lesser to the greater circulation. Riedel (1877) [25] injected oil into an artery, getting the most extensive embolism in the lung after the oil had passed through the other organs. He mentioned two factors in explanation: (1) the lower blood pressure in the pulmonary circulation, and (2) the lack of supporting tissue about the tortuous pulmonary capillaries.

Scriba,[24] noting the large amount of oil that could be injected without fatal effect, attempted to establish a ratio between the fatal dose and the amount of the depot fat. He calculated the fat content as 71 Gm. in a human femur, as 12.7 Gm. in that of a 17 Kg. dog and as 1.3 Gm. in that of a 2 Kg. rabbit. He found that a dog showed no threatening symptoms until one third of the entire body fat mass had been injected at one sitting and reported a similar relationship in the rabbit. Ribbert (1894),[26] estimated the fatal human oil dosage as 30-40 cc., but Landois (1923,[2]) accepting Scriba's ratio, computed the fatal human dose at 210 cc. Fibiger (1901) [27] reported the accidental injection of 50 cc. of oil into the vein of a young adult man; the victim died. Fibiger ascribed the death to fat embolism. Fuchsig (1902) [28] reported the fatal intravenous olive oil dosage for dogs as 2 Gm. per kilogram. Wegelin (1913),[29] after reference to the contention of Merckel that intravenous oil injection in dogs justified no conclusions as to human embolism, reported the work of Kojo on the relative effects of various oils. Kojo found that in rabbits an intravenous injection of from 0.6 to 0.7 cc. of olive oil per kilogram was well borne. A dose of 0.85 cc. per kilogram paralyzed the hind legs with recovery, whereas from 1 to 1.5 cc. per kilogram caused death. Using rabbit fat in the place of olive oil, he found 0.5 cc. per kilogram definitely fatal. Human fat in a dosage of 0.5 Gm. per kilogram was well borne, but 1 Gm. of human fat per kilogram would regularly cause death. The olive oil, Kojo found, went over into the greater circulation in considerable amount; rabbit fat injection gave only pulmonary embolism and human fat seemed to occupy an intermediate place as regards viscosity. Kojo found the reabsorption of emboli complete in three weeks. The homogenous fat was reab-

24. Scriba: Deutsche Ztschr. f. Chir. **12**:118, 1879.
25. Riedel: Deutsche Ztschr. f. Chir. **8**:571, 1877.
26. Ribbert: (Footnote 4, second reference.)
27. Fibiger, cited by Gröndahl (footnote 10) and others.
28. Fuchsig, cited by Warthin (footnote 1).
29. Wegelin, C.: Schweiz. med. Wchnschr. **53**:133 (Feb. 8) 1923.

sorbed more rapidly than the vegetable oil. Again in 1920 Miller [30] reported rapid reabsorption of oil injected in sublethal quantities and was able, by repeated injection, to get one dog to tolerate 260 cc. in a period of five weeks time.

Paul and Windholz (1925) [3] have reported work on the injection of human fat into the veins of rabbits. Repeated injection in nonfatal doses resulted in a nonprotein nitrogen retention as great as that in uremia. The blood sugar fell as low as in the insulin death of rabbits and the blood lipase did not rise. The injected fat was traced throughout the organs. It gave rise to an endothelial proliferation in the lungs and an increase in leukocytes. The fat was taken up by endothelial cells and histiocytes with the formation of giant cells. Blood pigment was deposited in the spleen. There were miliary hemorrhages and softenings in the brain. There was an increase in fat in the heart muscle fibers, in the renal epithelium, and in the Kupffer cells, and there was a parenchymatous necrosis in the liver, which was free from glycogen.

To summarize the significance of this experimental work is impossible. The foregoing review only emphasizes the absence of agreement on any phase of the problem and offers no single logical explanation to unify the varying clinical and pathologic findings.

## EXPERIMENTS

Our first experimental attack on this chaotic situation has been an attempt to establish the lethal dose of oil injected intravenously in dogs. Varying results recorded above make dependable observations obligatory. Before such observations become dependable they must be made in great number and with a variety of oils of different viscosities and melting points. So far we have used only cottonseed oil, and our experiments are few. They suggest, however, that a lethal dose can probably be determined.

Intravenous injection of sterile cottonseed oil (autoclaved) was done under aseptic precautions. The oil was injected with a syringe over a period varying from a few seconds to twenty minutes. The differences in rapidity of injection seemed to make no difference in the effects, although such a conclusion can be little more than an impression. Brief ether anesthesia was employed and the vein was exposed by a small incision which was afterward closed by a single silk suture. None of the wounds suppurated.

Table 6 shows the results of varying dosages of cottonseed oil in twelve dogs. Three dogs that received 2 cc. or more per kilogram died spontaneously within a few hours. Two dogs that received 1.7 and 1.66 cc. per kilogram, respectively, died within a few days. Six

30. Miller: Tr. Coll. Phys. Philadelphia **42**:25, 1920.

dogs that received 1.5 cc. per kilogram or less survived or were killed when in good health, for other reasons. Three of these six were allowed to survive and at the date of writing have remained in good health for more than two months. The dog that received the smallest dose, 0.34 cc. per kilogram, died spontaneously at the end of six weeks from lung suppuration. This dog was never robust and showed symptoms, diarrhea and a hacking cough, within ten days of injection. It is possible that an organism of low virulence was introduced with the oil by a break in aseptic technic. Certainly death can hardly be ascribed to the mechanical effect of the oil in view of the other results. It seems probable from these figures that the dog will tolerate an injection of sterile cottonseed oil intravenously to the amount of 1.5 cc. per kilogram.

TABLE 6.—*Results of Intravenous Injection of Sterile Cottonseed Oil in Dogs*

| Dog | Weight in Kilograms | Amount of Oil Injected, Cc. | Dosage of Oil per Kilogram, Cc. | Dogs Died Spontaneously | Dogs Killed Experimentally | Dogs Surviving |
|---|---|---|---|---|---|---|
| 27 | 7.6 | 23.0 | 3.0 | At 1 hour | ..... | ..... |
| 35 | 10.0 | 25.0 | 2.5 | At 3 to 12 hours | ..... | ..... |
| 36 | 12.2 | 24.5 | 2.0 | At 3 to 12 hours | ..... | ..... |
| 32 | 5.0 | 8.5 | 1.7 | At 11 days | ..... | ..... |
| 34 | 11.5 | 20.0 | 1.66 | At 18 days | ..... | ..... |
| 26 | 10.0 | 15.0 | 1.5 | ..... | Killed by pneumothorax at 1 hour | ..... |
| 31 | 6.0 | 9.0 | 1.5 | ..... | ..... | Living and well at 72 days |
| 37 | 8.6 | 13.0 | 1.5 | ..... | ..... | Living and well at 59 days |
| 33 | 7.5 | 9.0 | 1.2 | ..... | ..... | Living and well at 67 days |
| 29 | 5.4 | 4.5 | 0.83 | ..... | Killed at 7 days | ..... |
| 30 | 5.0 | 4.0 | 0.8 | ..... | Killed at 7 days | ..... |
| 28 | 6.2 | 2.1 | 0.34 | At 43 days | ..... | ..... |

Figures 20, 21 and 22 show the amount of fat respectively in the lung, medulla and kidney of dog 27, which died an hour after injection of 3 cc. of cottonseed oil per kilogram. They are interesting chiefly for comparison with the photomicrographs of nontraumatic fat embolism caused by ether administration. Figures 23 and 24 show the amount of fat that may remain in the capillaries of the lung and kidney a week after injection. This dog (dog 30) received only 0.8 cc. of cottonseed oil per kilogram. It was killed at seven days for the purpose of estimating the rate of disappearance of the oil from the blood vessels. We are not reporting at this time the pathologic observations on the dogs dead following oil injections on account of the small number available for study.

Fig. 20.—Lung of dog 27 after intravenous cottonseed oil injection, 3 cc. per kilogram, under low power (sudan III).

Fig. 21.—Medulla of dog 27 after intravenous cottonseed oil injection, 3 cc. per kilogram, under low power (sudan III).

We were struck by the fact that, if the human being can be compared to the dog, a man of 60 Kg. could tolerate the amazing quantity of 90 cc. of cottonseed oil, and a man of 80 Kg., a not uncommon weight, could tolerate 120 cc. Ignoring for the time the differences in viscosity and melting points between human marrow fat and cottonseed oil, we then calculated the available fat in the marrow of the femur. Later we encountered Scriba's similar calculations and identical reasoning, as summarized above, and were satisfied to find fair agreement.

We first split the femora of three skeletons. These were respectively 47.2 cm., 49.4 cm. and 48.6 cm. in length, corresponding to heights of 6 feet 3 inches, 6 feet 4 inches and 6 feet 4 inches. This calculation is

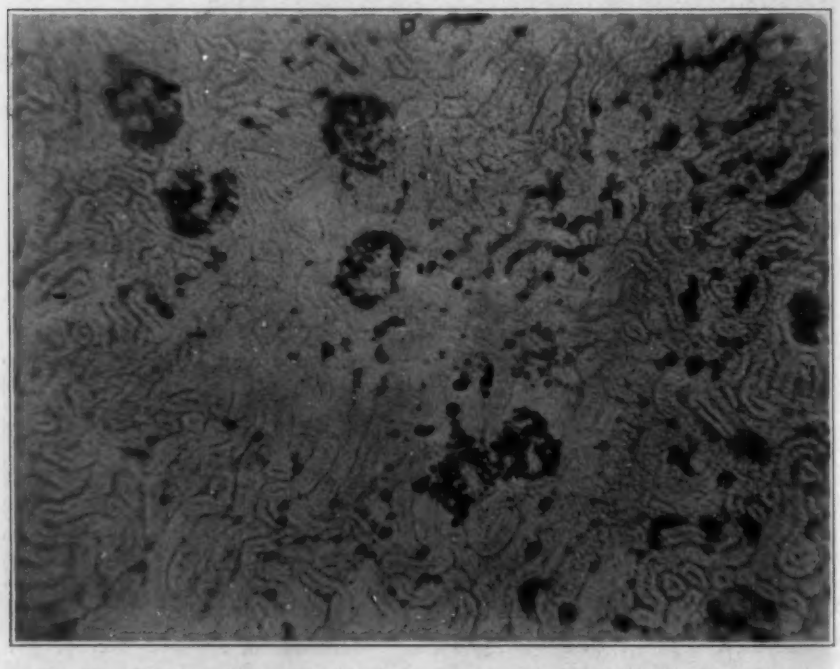

Fig. 22.—Kidney of dog 27 after intravenous cottonseed oil injection, 3 cc. per kilogram, under low power (sudan III).

based on Martin's citations [31] that the femur is approximately one fourth the total length of the body. We can reduce these rather excessive heights to a uniform 6 feet and still deal with persons whose weight must be at least 75 Kg. The open marrow cavities of these bones were then measured, exclusive of the definitely cancellous portions, and the capacities were calculated. The capacities of the three marrow cavities were respectively 96.2 cc., 106.7 cc. and 96.2 cc., an average of 99.7 cc.

31. Martin: Lehrbuch der Anthropologie, Jena, 1914, p. 254.

We then cut measured segments from two freshly amputated femora and calculated the capacity of the marrow cavities. The fat in the marrow was melted out, measured, and 10 per cent added for possible error. From these two calculations we found that in the one instance 50 per cent of the marrow cavity content was fat and in the other instance, 63 per cent.

Applying the larger of these figures, which more nearly approaches Scriba's measurements, to the average complete marrow capacity as calculated above, we find that the marrow cavity of the femur of a 75 Kg. person contains approximately 65 cc. of fat. This corresponds to 0.86 cc. per kilogram.

The significance of these calculations now becomes apparent. If the difference in effect between marrow fat and cottonseed oil is not great, and if man can tolerate oil as easily as the dog, then one should be able to pour into the veins all the fat from the marrow of a single femur without causing symptoms.

The fundamental contradiction is clearly presented by this example. Several solutions, any or all of which may be effective, can be proposed:

1. Is there a difference in susceptibility to fat between dog and man?

2. Is the difference between cottonseed oil and marrow fat sufficient to make so great a difference in threshold value?

3. Is there an additional source of the fat in traumatic fat embolism, other than the depot fat? (Our results in Part I suggest that this may be so.)

4. Do symptoms depend on some law of distribution of fat emboli, dependent, perhaps, in differences in the architecture of the vascular tree between dog and man, such as the absence in the dog of the internal carotid artery?

5. Do symptoms depend on chance distribution of emboli to vital centers?

6. Has it been established without question that symptoms ascribed to fat embolism are really due to that cause, and not to other disturbances of physiologic balance?

In regard to this last query we report an interesting observation. None of the dogs that received intravenous injections of cottonseed oil developed pulmonary edema that could be detected clinically, even when as much as 3 cc. per kilogram was given. The high proportion dogs, however, showed the gross and microscopic lung changes of pulmonary edema. In the classical clinical description of fat embolism, pulmonary edema as a symptom is given much weight.

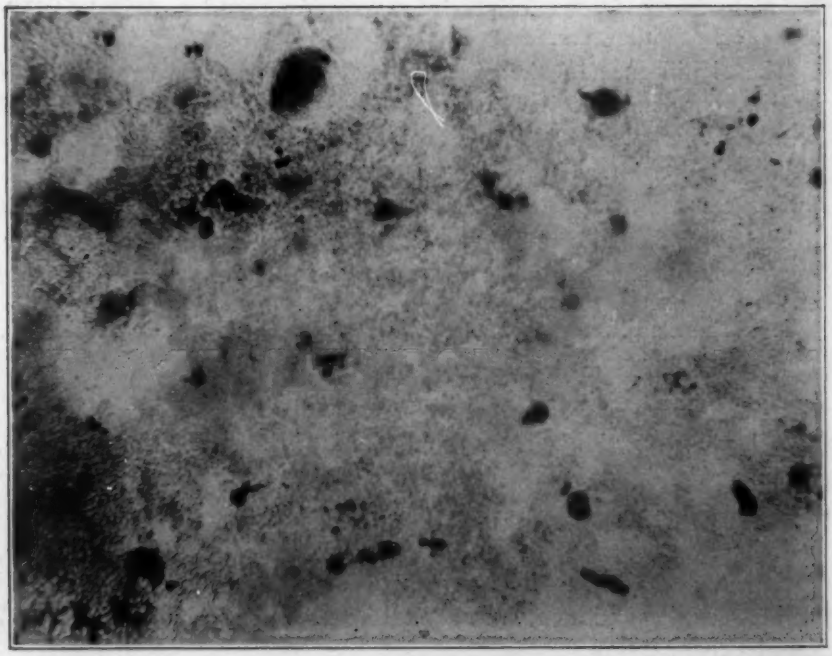

Fig. 23.—Lung of dog 30 after intravenous cottonseed oil injection, 0.8 cc. per kilogram, under low power (sudan III); the dog was killed one week after the injection.

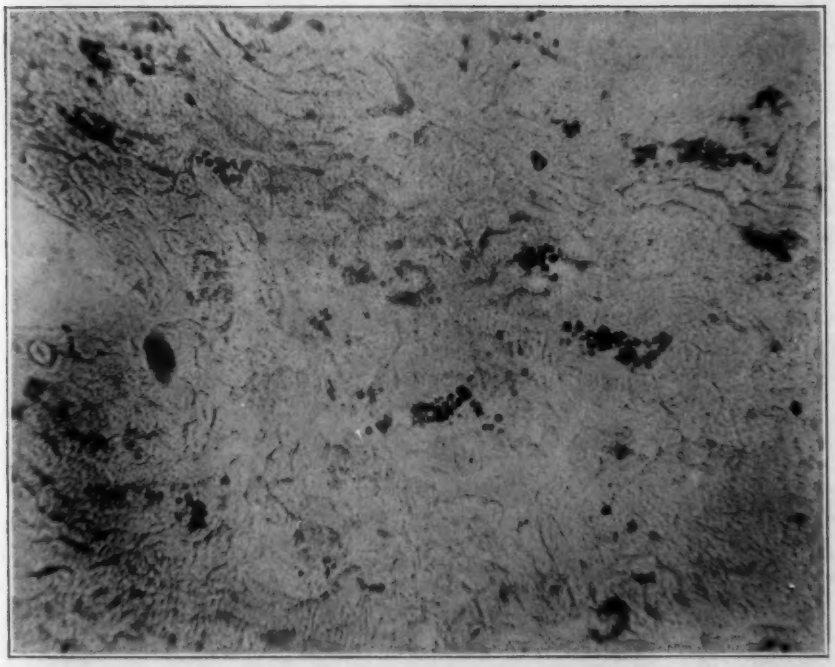

Fig. 24.—Kidney of dog 30 after intravenous cottonseed oil injection, 0.8 cc. per kilogram, under low power (sudan III); the dog was killed one week after the the injection.

One further comment may be made on the quantitative factors of this problem. Assuming 7 per cent of body weight to be blood, a 75 Kg. man has 5,250 cc. of blood. We have said that the blood fat normally may range as high as 2 per cent. This man then has 105 cc. of fat in his blood. If the percentage is greater, as it may be in an intense digestive lipemia or in disease, the amount of circulating fat is correspondingly increased. From this it is evident that an effective breakdown of the plasma emulsion as suggested in Part I of this paper will furnish easily as much fat for embolic lodgment as will the marrow of a broken femur.

As we state in the introduction to this part of the paper, we are basing no conclusions on the few experiments here recorded. We intend only to present the problem for future study.

# THE UNDESCENDED TESTIS

## AN EXPERIMENTAL AND CLINICAL STUDY *

OWEN H. WANGENSTEEN, M.D.

MINNEAPOLIS

It is now generally believed that the undescended testis is usually incapable of a continued production of spermatozoa. Hunter,** [123] who first described the normal descent of the testis, stated that failure of the testis to reach the scrotum is due to its initial imperfection. Most European investigators hold to this opinion. But operations are continually being performed on the undescended testis in the hope that with transference to the scrotum that spermotogenesis will occur. If the development of the testis is not altered by transition to the scrotum, only the belief that the danger of malignancy is lessened or that the patient is more pleased with his testis in its usual habitat would justify operative interference in the absence of pain or other complicating factor. A decision as to whether the testis is ab ovo deficient or whether its abnormal situation is responsible for its lack of development is therefore of paramount importance in the rational treatment of the undescended testis.

Orchidopexy is an old procedure and it would seem that the examination alone of those cases in which the operation has been done for failure of both testes to descend would determine whether or not an undescended testis would develop normally if placed in the scrotum. Records of results are numerous, as concerns the position of the transplanted organ, and many observers [16, 43] record an increase in size after scrotal fixation. But reports concerning examination of the semen when the operation has been done for double incomplete descent are unfortunately few, so few in fact that it could with just cause be claimed that these are merely examples of those rare instances in which a temporary spermatogenesis occurs in cryptorchids.

A sufficient number of such cases have now been recorded that one cannot deny that spermatogenesis [250] may occur in cryptorchids. Marechal [174] in 1887 was able to compile fifty cases in which histologic examination of the removed organ or semen examinations in double incomplete

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* From the Department of Surgery, University of Minnesota Medical School.

** Dr. R. E. Scammon informs me that Zerkis in 1495 had previously described the descent of the testis, but the first adequate description was given by John Hunter.

descent disclosed the presence of sperm. Taylor [266] in discussing the medicolegal aspect concerning the fertility of cryptorchids enumerates a number of cases in which the procreative power of such persons has been unquestionably established. A few writers would have us believe [42], [281] that it is the rule for testes retained within the abdomen to be quite normal. Uffreduzzi [277], [278] says that 10 per cent of cryptorchid testes exhibit spermatozoa. Rawlings [217] states that in fifty undescended testes removed at operation twenty-seven were examined microscopically and of these ten were fairly normal and showed a definite spermatogenesis. Odiorne [201] and Simmons examined seventy-seven postpuberty undescended testes and all of these showed degenerative changes. They report one instance of fertility in a man of 20 when neither testis was in the scrotum. Bland-Sutton was only able to find spermatozoa once in the histologic examination of twenty-five incompletely descended testes. Lanz [158] saw spermatozoa once in eleven testes that failed to reach the scrotum. Griffiths [112] doubts the authenticity of every case in which spermatogenesis is said to have occurred in bilateral incomplete descent, and doesn't believe that the retained testis can produce spermatozoa. In practically every instance in which speramatozoa have been demonstrated in the examination of cryptorchids the subject has been young.[286] So constant has this finding been that one theory as to the nature and behavior of the undescended testis depends for its explanation on this factor.

Monod and Arthaud,[187] on the basis of finding a fairly normal histology in the undescended testis of a man of 20 and atrophy in two men over 40, promulgated the idea that incomplete descent is compatible with fecundity in the young but that with increase in age an atrophy slowly and progressively occurs.

Two other opinions as to the condition of the incompletely descended testis have been given credence by those who have investigated this problem. Curling [64] held that undescended testes developed normally to puberty, then failed to undergo the changes incident to this age and remained in the prepuberty stage. Histologic study, however, demonstrates that a real degenerative process is observed in the ectopic testis with the supervention of puberty.

Hunter [130] believed that the aberrant position and absent spermatogenic function were both due to congenital imperfections and that "nothing can be done by art to give the testicles the stimulus of perfection which is necessary to make them assume the disposition requisite for their descent." Hunter's opinion today claims as adherents numerous supporters and investigators. Bland-Sutton [22] states, "A testis is retained because it is imperfect. The migratory impulse in a healthy, normal testis is irresistible"; and again, "The imperfections of an undescended testis are the cause, not the consequences of its failure

to reach its goal in the scrotum. . . . Surgical efforts to preserve a retained or a partially descended testis may be described as supererogation." At a recent meeting of the Royal Society of Medicine in London, Bland-Sutton [24] reiterated his previous stand and said that "the notion that the functional imperfection of a retained testis is due to its nondescent is false." Eccles [76] at the same time said that it was wrong to speak of atrophy and that an undescended testis is underdeveloped. Finotti [94] also shares this opinion. Uffreduzzi [277] describes nondescent as a local expression of infantilism. Recent investigations on the continent seem to bear out Hunter's theory. Staemmler [254] believes that a hypoplasia of the spermatic arteries is the cause of lack of development and also prevents descent. Schinz and Slotopolsky [234] state that cryptorchidism is essentially a hypoplastic process and that this hypoplasia is only a part of a general developmental disturbance "vitium primae formationis."

It has, however, long been felt by many that given the advantage of the natural environment that the scrotum affords an incompletely descended testis would develop normally and that the success or failure of the scrotal fixation would be a dominant factor in determining the future possibilities of the imperfectly descended organ. The almost universal practice of orchidopexy therefore signifies that many still cling to the belief that failure to reach the scrotum accounts for the aspermatic condition of the undescended testis.

Is has been my object in this study to investigate the merits of these two controversial opinions. If the incompletely descended testis owes its imperfect development to its failure to descend, a successful orchidopexy would rectify the condition and stamp the operation as being of material and functional benefit. Failure of the germinal epithelium to develop would indicate that the object of the procedure is only cosmetic. These two diametrically opposed ideas cannot be compromised. Does transition to the scrotum enable an imperfectly descended testis to develop normally or is it *ab initio* imperfect and incapable of mature growth?

## MODE OF INVESTIGATION

In the study of this problem several testes that failed to reach the scrotum and were removed in the course of operations for hernia in adults have been examined. Normally descended testes removed in the radical cure of large hernias and hydroceles have also been submitted to examination. Testes of young pups and adult dogs have been placed in the peritoneal cavity and the inguinal region and the effect on the organ noted. After having been allowed to remain in the peritoneal cavity or inguinal region for a given period, a number of

testes have been redeposited in the scrotum. The influence of severance of the blood vessels in the spermatic cord and ligation of the vas deferens has also been noted. Special study has been given the anatomy of the prepuberty testis.

### DESCENT OF THE TESTIS

The abdominal position of the fetal testis was first mentioned by Haller.[130] Frankl [98] states, however, that this was also known to Galen. Hunter,[130] who first described the normal descent of the testis, was at a loss for a satisfactory explanation. Many of the early investigators attributed it to the action of the cremaster.[270] Edwards [77] says that the gubernaculum shortens with descent and turns about much as can the finger of a glove. Hart [24] speaks of the gubernaculum as a rudder. Keith * states that the gubernaculum in drawing the peritoneum down drags the testis with it like a log on a sledge. That the gubernaculum has little or no active part in the descent of the testis becomes evident in the cases in which the testis is in the scrotum, but there is an absence of fixation [279] to the scrotum by the gubernaculum.

The testis develops on the inner side of the wolffian ridge in close relation with the kidney and remains intra-abdominal in position [29] throughout the greater portion of fetal life. Scammon [232] divides the transition of the testes to their scrotal position into three stages. In the sixth week of fetal life, the genital ridge extends from the sixth to the twelfth dorsal segments. During the third month, because of an atrophy of the cranial segments, the definitive testis lies in the iliac fossa. As a consequence of unequal rate of growth of structures below and above the inguinal ligament, the testis comes to lie at the future internal abdominal ring. These two phases of descent are entirely passive. Preceded by the vaginal process of peritoneum, the testis passes obliquely through the abdominal wall, reaching the external abdominal ring during the seventh or eighth month. In over 90 per cent of new-born children the testis has arrived at the bottom of the scrotum. The scrotum, a derivative of the abdominal wall, is preformed to receive the testis. At birth the upper portion of the vaginal process is obliterated,† but the lower end persists throughout life as the tunica vaginalis propria. Failure of this peritoneal tunic to obliterate in the upper portion constitutes a potential inguinal hernia. The passage of the testis through the abdominal wall is an active migation, but Scammon [232] states that there is no known cause adequate to account for this stage of descent.

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* Human Embryology and Morphology, New York, 1921, p. 399.

† For an excellent discussion of the obliteration of the vaginal process reference should be made to Engel,[81] Frankl,[98, 99] Lockwood,[130] Sachs [225] and Zuckerkandl.[299]

The testis may be arrested in its descent at any point, most frequently in the inguinal region and almost as often at the external abdominal ring. It may remain in the abdominal cavity in the iliac region or descend into the perineum. Femoral ectopy of the testis has been described but Eccles [72, 73] considers its existence doubtful. He states that in almost every instance the testis passes through the canal and passes into the upper portion of the thigh through the external abdominal ring. In transverse ectopy of the testis both organs occupy one side of the scrotum. This abnormality may be due to faulty development or faulty descent. In event the former condition obtains both testes develop on the same side; in the latter they descend through the same inguinal canal but develop from genital buds on opposite sides. This abnormality of descent was first described by Lenhossek.[162] Kimura [143] compiled ten such cases from the literature and reported another in 1918. Pubopenile ectopy of the testis [134] is also very rare. Two cases [95, 197] have recently been reported. Perineal ectopy has been ascribed to a vicious insertion of the gubernaculum, and to being pushed into an abnormal position by a hernia. Weinberger [289] in 1899 was able to find seventy-three cases of this type. He did not believe that the action of the gubernaculum accounted for the descent of the testis into the perineum. In 1906 Klein [144] reported eighty-one cases of perineal testes. According to Sonneland,[251] the superficial inguinal type of interstitial ectopy, the perineal and the pubopenile may all be accounted for as types of incomplete descent in which the testis has passed out through the external abdominal ring but failed to reach the scrotum. In interstitial hernia the testis may be carried up over the abdominal wall above or beneath the external oblique aponeurosis or less commonly beneath the internal oblique. Krönlein [149] early pointed out the frequent association of incomplete descent of the testis with this type of hernia. Eccles [74] states that in 73.4 per cent of cases arrest of descent is associated with inguinal hernia.

Ectopy or an abnormal situation outside of the usual path of descent is considerably less frequent than incomplete descent. Monod and Terrillon [188] ascribe to Kocher this differentiation between ectopy and incomplete descent.

## FREQUENCY OF UNDESCENDED TESTES

Statistics of the Austrian army [301] show that for every thousand men drafted for military service, 2.2 have an undescended testis. Rennes [220] observed six cases amongst 3,600 recruits. Marshall [177] found eleven in 10,800. The war department medical records [287] for the World War show that there are 3.1 cases of incom-

plete descent * for every thousand cases examined. Double incomplete descent [188] is incomparably more rare than single and right sided arrest of descent occurs more commonly than it does on the left. This is in agreement with the fact that the left testis usually descends earlier than the right.

Only rarely does the testis reach the scrotum by its own initiative if it has failed to do so at the end the first year. Neugebauer reports thirty-eight cases of late descent.[128] With the increasing obliquity [40] of the inguinal canal due to the growth of the pelvis, the possibility that the testis may migrate spontaneously to the scrotum decreases greatly. Occasionally a testis that has been in the scrotum will return to the inguinal region. This is known as "ectopie en retour." [128] Stefko [257] has recently described the finding of a high percentage of inguinal testes in starving children (27 per cent). He attributes this finding to too short a cremaster occasioned by starvation in which an unequal growth of the muscles of the abdominal wall occurs.

### CAUSE OF FAILURE OF THE TESTIS TO DESCEND

Undoubtedly a number of factors may operate to bring about incomplete descent of the testis. Eccles [75] classifies the conditions that may be causative as follows:

1. Conditions associated with the mesorchium.
2. Those associated with the testis and its component parts.
3. Conditions associated with the gubernaculum.
4. Conditions associated with the cremaster.
5. Those associated with the route along which the testis must pass.

In by far the majority of cases of inguinal retention, however, separation of the spermatic cord from the processus tunica vaginalis testis suffices to mobilize the gland so that it may be placed in the bottom of the scrotum.[25, 45, 171, 212] Bevan [16] states that separation of the peritoneum from the vas deferens and spermatic vessels, if carried from 2 to 3 inches (5 to 7.6 cm.) within the abdominal cavity and combined with removal of all the coverings of the cord, so that the testis hangs suspended by the vas and vessels alone, will so mobilize the testis that in many instances it may be placed on the thigh several inches below the inguinal ligament. Bevan [19] says that in only 10 per cent of cases has it been necessary to section the vessels in the pampiniform plexus in order to bring the testis into the scrotum. Büdinger [38, 39] states that the vessels are always short and cites the relation that obtains in

* This figure includes anorchism and monorchism. Absence of the testis is an exceedingly rare anomaly and it is scarcely possible during life to obtain reliable proof concerning its existence. Jacobsen [334] says that Gruber in 1868 could compile only twenty-three cases of unilateral anorchism and seven of the bilateral variety, all having been verified by necropsy.

ectopic kidneys. The vas deferens is always long enough he finds, but the vessels are no longer than they need to be for the position of the testis. The most common cause of retention of the testis he ascribes to peritoneal adhesions [38] occasioned by fetal peritonitis or inflammation in early postembryonic life. Bramann [30] and Robitansky have each observed a case in which shortness of the vas prevented the testis from reaching the scrotum. According to a few investigators, [106, 277] heredity plays a dominant rôle in bringing about nondescent of the testis.

## THE ANATOMY OF THE NORMALLY DESCENDED TESTIS AND OF THE UNDESCENDED TESTIS

The testes are bluish white ovoid bodies suspended in the scrotum (about 25 Gm. each in weight). The tunica vaginalis testis ensheaths the whole testis anteriorly: on its posterior aspect where this tunic is deficient the testis is capped by the epididymis. Here also the vessels leave the testis. Beneath the visceral lamina of the vaginal tunic investing and fused with the testis is the tough tunica albuginea. From the deep surface of this covering a number of slender fibrous bands dip into the gland. These septula testes imperfectly divide the parenchyma [71] into a number (from 100 to 200) of wedge shaped lobules whose apexes converge toward the mediastinum testis at the posterior border of the gland. The parenchyma of the organ is composed of large numbers of manifoldly twisted tortuous seminal canals which may anastomose [81] with one another. These, the seminiferous tubules (about 600) completely fill up the spaces between the septums and are loosely held togther by connective tissue. At the apexes of the lobules they unite to form the straight tubules, short narrow seminal canals which open into a complicated network of fine channels known as the rete testis in the mediastinum. Out of this network from about fifteen to twenty minute tubules,[71] the efferent ductules of the testis, pierce the tunica albuginea at the upper end of the posterior margin and enter the caput epididymidis. After an unusually tortuous course, these ducts end at the cauda epididymidis by becoming the vas deferens. The latter, the excretory duct of the testis, begins as the continuation of the ductus epididymidis and ends by uniting with the excretory duct of the seminal vesicle to form the ejaculatory duct emptying into the urethra in its posterior portion.

The minute anatomy of the testis shows it to be a tubular gland with a loose interstitium separating the tubules. Each seminiferous tubule in the adult testis contains several layers of epithelial cells. The Sertoli or nourishing cells lie directly on the basement membrane of the tubule. They have no part in the spermatogenic cycle. They are elongated irregularly pyramidal cells [71] with large oval nuclei rich in chromatin. The cytoplasm of these cells has a high fat content.[118, 119] Toward the periphery

of the tubule and scattered between the Sertoli cells are the spermatogonia, the progenitors of the adult male sex cell. In the prepuberty testis, the Sertoli cells and the spermatogonia are the only cells lining the seminiferous tubules. In the mature testis, the spermatogonia are small round elements with nuclei rich in chromatin. By growth the spermatogone becomes a spermatocyte of the first order. These divide and form two secondary spermatocytes whose division gives rise to the spermatids from which the spermatozoa takes origin.

In the intertubular spaces there are groups of cordlike masses, the interstitial cells.* These are rounded polygonal elements with small eccentric nuclei. Scattered in the finely granular cytoplasm may be found pigment particles or crystalloid bodies [211] in the form of minute rods or needles.

The main artery of the testis is the internal spermatic which takes origin from the abdominal aorta. In addition it is also supplied by the deferential and external spermatic arteries which establish anastomoses with the internal spermatic. The testicular branches enter the mediastinum and break up into superficial and deep twigs that follow the tunica albuginea and the septums, respectively. The latter follow the tracts of intertubular connective tissue and ultimately form rich capillary networks enclosing the seminiferous tubules outside the basement membrane. The veins arise in these networks and emerge at the mediastinum and together with the veins from the caput epididymidis ascend in the spermatic cord in the anterior part of the pampiniform plexus. The veins from the body and tail of the epididymis unite into a smaller group that ascend in the posterior part of the plexus.

The lymphatics of the testis follow the course of the veins and drain into the lumbar lymph nodes. The nerves of the testis are chiefly sympathetic fibers that follow the course of the internal spermatic artery.

The histology of the immature testis and the blood supply of the organ will be dealt with more fully later.

The retained testis of the adult when compared with its normally descended fellow, though preserving the contour of the normal organ, is of much smaller proportions. But apart from this disproportion in size the gross anatomy of the normal organ is preserved.[91] Occasionally the body and tail of the epididymis remain separated from the testis by the mesorchium.[39, 140]

When examined microscopically, however, a remarkable difference in structure is at once apparent. The singular disappearance of the germinal epithelium from the seminiferous tubules is most striking.

* Odiorne and Simmons [210] and Coley [49] state that there are no interstitial cells in the normal adult testis. Winiwarter,[208] however, finds them present and Benoit [33, 34, 35] states that failure to observe them is due to lack of proper tissue fixation.

Frequently only the bare outline of the tubule persists as a hyaline ring. Many have a single layered epithelium constituted only by the Sertoli cells. No spermatogonia or other sex cells are usually present. In the retained testes of individuals just past puberty, however, spermatogonia and spermatocytes are not infrequently found. In seventeen undescended testes that I examined microscopically, spermatozoa were never observed. But in several fairly young subjects spermatogonia were often present. The number of prepuberty undescended testes that have been examined are, as might be supposed, very rare. In the instances in which this has been done, however, the degenerative changes that occur in the post-puberty testes are absent and the histology of the gland is much the same as a normally descended organ of a similar age.[20, 86, 89] This matter will be discussed at more length in the consideration of the anatomy of the immature testis. The interstitial cells in the atrophic adult incompletely descended testis appear increased in number. It has been felt that this apparent increase is real, but recent quantitative measurements by Bascom [9] would indicate that no real increase occurs.

## COMPLICATIONS TO WHICH THE UNDESCENDED TESTIS IS LIABLE

*Pain.*—The incompletely descended testis is subject to the same diseases that affect the normally placed organ. Failure of the testis to descend completely may give rise to no subjective symptoms. Inguinal retention of the testis may be associated with pain. The abnormal position in such an event renders it especially liable to traumatism and recurrent attacks of pain due to this cause are not infrequent.[286]

*Hernia.*—It is usually an associated hernia that urges the patient with incomplete descent to seek medical aid.[53] An inguinal hernia may occur if the testis is retained within the abdomen because the processus vaginalis testis [29, 128] precedes the testis in its normal descent into the scrotum. Coley [51] states that in 80,736 cases treated for hernia 1,357 were complicated by undescended testes. Eccles [73] reports 854 cases in which arrest of descent was present in 48,000 cases of inguinal hernia. Uffreduzzi [277, 278] states that in 90 per cent of cases of incomplete descent there is an associated hernia. Schönholzer [238] finds a hernial sac present in 93 per cent; Rawlings in 75 per cent; [217] Odiorne and Simonds [201] in only 57 per cent; Rovsing [227] in 100 per cent of cases of failure of the testis to complete descent. In probably every case there is a potential hernia due to a persistent tunica vaginalis testis.

*Torsion.*—Nicoladani * called attention to the fact that the undescended testis is more liable to rotation of its pedicle with torsion and subsequent strangulation than the normally descended organ. In 1901

* Nicoladani: Arch. f. klin. chir. **31**:178, 1885.

Scudder [242] compiled thirty-two cases of torsion of the pedicle of the testis. Forty-seven per cent of these occurred in undescended testes.

*Malignancy.*—Nearly all who have written on the subject of malignancy in the testis are agreed that the incompletely descended organ is more likely to become malignant than the scrotal testis. Malignancy of the testis is a rare disease.[21, 237] In 1922 Tanner [265] stated that only about 600 cases had been reported in the literature. Of 452 cases compiled by Cunningham,[63] 412 had occurred in the normally descended testis. Malignancy in this series therefore was 10.3 times more frequent in the scrotal than in the undescended testis. When, however, allowance is made for the fact that only one testis in 500 is undescended, it is apparent that in Cunningham's [63] series, at least, the undescended testis is fifty times more likely to malignant degeneration than is the normally descended testis.

Tanner [265] believes that the testis retained within the abdomen is less likely to become malignant than is the normally descended testis. Bulkley [41] states that about one testis in seventy-five retained within the abdomen will become malignant, and that one out of every four malignancies in undescended testes is found in the abdomen. Several believe that the testis within the abdominal cavity enjoys an immunity from malignancy and that when an inguinal testis cannot be placed in the scrotum that it can with safety be placed in the abdominal cavity behind the peritoneum.[128, 238] A few writers state that this is the operation of choice in the treatment of undescended testes,[159, 281] and that an imperfectly descended organ is as likely to function there as in the scrotum. Uffreduzzi [278] and Keyes and MacKenzie [142] state that the abdominal testis is more likely to become malignant than the testis retained in the inguinal region. Malignancy has never been observed in a perineal testis.[144]

No greater diversity of opinion probably exists concerning anything in medicine than the question of malignancy in the undescended testis.

The opinion prevalent today that the abdominal testis is less prone to become malignant than an inguinal testis or one normally situated I believe to be but a heritage from earlier literature.[84, 137, 256] In 1893 Farwick [84] could find only three cases of malignancy in the testes retained within the abdomen and seventy-seven in inguinally retained testes. In 1901 Kaeppelin [137] could find only six malignant abdominal testes. Bulkley [41] in 1913 reported fifty-nine cases of malignancy in the abdominally retained testes. Cunningham [63] in 1921 stated that three had been reported since the appearance of Bulkley's paper. I have observed two cases of malignancy in the abdominal testis. Malignancy of the abdominally retained testis in the male hermaphrodite is not infrequent. Zacharias [300] mentions thirteen cases, two of which were bilateral.

Bland-Sutton [24] says that thirty-five have been reported. Romiti [225] reports the case of a man at thirty-seven who had a malignant abdominal testis. Eleven years previously during the course of a hernia operation the testis which had previously been scrotal in position was placed in the retroperitoneal region in order to better treat the hernia.

When it is recalled that malignancy is a rare disease in the testis, that an undescended testis is also infrequent, and that abdominal retention of the testis occurs with considerable less frequency than does inguinal retention, it must be conceded that an abdominal situation of the testis is not a protection against malignancy.

It has long been felt that the exposed position [70, 245] of the inguinal testis to trauma renders it susceptible to malignant change. The relative frequency of torsion in the inguinal testis has been pointed out. Kahlden [138] believes that the contraction of the abdominal muscles over the testis in the inguinal region, as occurs with coughing, lifting, etc., is responsible for the frequency with which malignancy is observed in the inguinal testis. Landau states that the contraction of the abdominal muscles over an inguinal testis could exert but little pressure on the gland.[277]

Coley [52] believes that trauma is a factor in one third of the cases of malignancy of the testis. Chevassu [47] states that traumatism favors the growth of a tumor but believes that trauma as a causative factor in testicular malignancies has been over rated.

In the undescended testis, the anatomic peculiarities * observed are the disappearance of the germinal epithelium and a hyperplasia of the interstitial cells. It has been suggested that the relative frequency of malignancy in undescended testes takes origin in these cells,[62, 29] but sarcoma of the interstitial cells [83] is a very rare tumor. A benign tumor † arising in the interstitial cells is not uncommon.

Wilms [292] stated that the complex malignant tumors of the testis contained all three germinal layers and were best considered as teratomas. Ewing [82] from a careful study of nineteen cases and an examination of the literature on the subject states that "the great majority or possibly all of these tumors are of teratomatous origin." Ewing [82] had several thousand serial sections made of embryonic testes through the corpus Highmori and rete testis. Several islands of chromaffin tissue and two misplaced groups of squamous epithelium were found. Ewing concludes "that teratoma testis arises from sex cells in the neighborhood of the rete, whose normal development into spermatogonia has been suppressed but whose potencies remain intact or ready to express themselves in the various forms of simple or complex teratomata."

* It has erroneously been maintained that an ectopic perineal testis [29, 290] is histologically normal.

† It is said to occur frequently in old dogs.[108]

The relative frequency of malignancy in the undescended as compared with the normally descended organ is best accounted for in Ewing's explanation of the mode of origin of malignant testicular tumors.

Prophylactic removal of an inguinal testis because of the danger of malignancy is scarcely warranted. Such a procedure has not been applied to other organs in which malignancy is manifoldly more common.

Several instances have been reported in which tumors have occurred in the normally descended testis while the same patient carried one in which only partial descent had occurred. Howard [129] records the instance of a man of 37 the subject of a carcinoma of the testis. At 7 his testis was in the scrotum; as a result of trauma dislodgement occurred into the inguinal region. The converse has also been noted. Cunningham [63] reports the case of a man of 30 the subject of a teratomatous testis. At 25 this testis had been in the inguinal region and at that time was placed in the scrotum. Coley [51] reports an instance in which malignancy of the testis followed closely on replacing the testis in the scrotum. Tyrell [276] mentions the case of a man whose left testis descended into the scrotum spontaneously at 20. Twenty-five years later, at 45 years, a sarcoma developed in this testis. Marlier [175] mentions such an instance in a man whose left testis first descended into the scrotum at 16; at 38 the testis was the seat of a carcinoma. Romiti [225] relates the history of a man of 37 who developed a malignancy in a testis once resident in the scrotum that eleven years previously was placed in the abdomen in order to cure a large inguinal hernia.

Orchidopexy therefore does not diminish the possibility of a malignancy developing in the testis with reposition of the organ into the scrotum.

## EXPERIMENTAL INVESTIGATION

All experiments were done on dogs (a few early experiments not recorded were done on guinea-pigs and rabbits) under usual aseptic technic. Ether was used to obtain anesthesia. Fine linen sutures were used throughout. The experiments will be tabulated according to type of procedure instead of in chronological sequence. The examination of the undescended testes and the testes removed in the course of operations for the cure of hernia and hydrocele, and those obtained from persons dying of acute febrile and chronic debilitating diseases will be recorded following tabulation of the procedures on dogs. Formaldehyde fixation (10 per cent) of tissue and hematoxylin and eosin stains were used. All tissue was embedded in paraffin and the sections were cut from 8 to 10 microns in thickness.

## TRANSPLANTATION OF TESTES OF MATURE AND YOUNG DOGS INTO THE ABDOMINAL AND INGUINAL REGION

### SERIES I

EXPERIMENT 1.—July 1, 1923, large adult dog.

Abdominal reposition was made of both testes through oblique incisions in both inguinal regions. The spermatic cord was freed and the internal ring enlarged on both sides. The gubernacula were severed, the peritoneal cavity was opened on both sides and the testes were pushed into the abdomen. On the left, the tunica vaginalis testis was removed; on the right side it was left intact. The wounds were closed in layers.

After the lapse of two months, this dog was kept with two adult female dogs for a considerable length of time without impregnating them.

December 28, 180 days later, castration was done. The wounds had healed well. The left testis was free in the peritoneal cavity; the right was ensheathed in omental adhesions. There was no interference with the vascular supply of either testis. Grossly both testes were markedly reduced in size. The tunica albuginea was thickened. Microscopically there was total loss of the germinal epithelium. Only Sertoli cells remained within the seminiferous tubules. In some of these, the nuclei were small and the cells gave the appearance of empty sacs. Many of the tubules were distorted. The interstitial cells appeared quite prominent.

EXPERIMENT 2.—July 5, 1923; an adult dog.

Abdominal reposition was made of both testes through inguinal incisions. The tunica vaginalis testis was left intact on both sides.

July 11, six days later, the dog was killed. There was a small hematoma in the right wound; the left was well healed. The right testis was free in the peritoneal cavity at the brim of the pelvis. The left testis was free except for slight attachment to the great omentum. Both testes were somewhat smaller than at operation.

Microscopically, there was definite loss of the germinal epithelium within the tubules. Numerous giant cells and débris occupied the lumina of the tubules. The interstitium was normal.

EXPERIMENT 3.—July 9, 1923; an adult dog.

Abdominal reposition was made of the right testis. The left testis was not touched.

July 14, five days later, castration was done. There was the same picture as in dog 2. The left testis showed normal spermatogenesis.

EXPERIMENT 4.—July 27, 1923; an adult dog.

Abdominal reposition was made of both testes through inguinal incisions.

August 6, ten days later, castration was done. The loss of germinal epithelium was a little more definite than in dog 2. Giant cells and necrobiotic changes were evident in all tubules. In many most of the sexual cells had disappeared. There was considerable peritubular edema.

EXPERIMENT 5.—Feb. 20, 1925; an adult dog.

Both testes were put into the peritoneal cavity through inguinal incisions.

April 13, fifty-two days later, castration was done. The testes were reduced in size; the tunica albuginea was thickened; the germinal epithelium was gone. Only a single row of Sertoli cells remained in the tubules. No products of necrobiosis were present. The interstitium was normal.

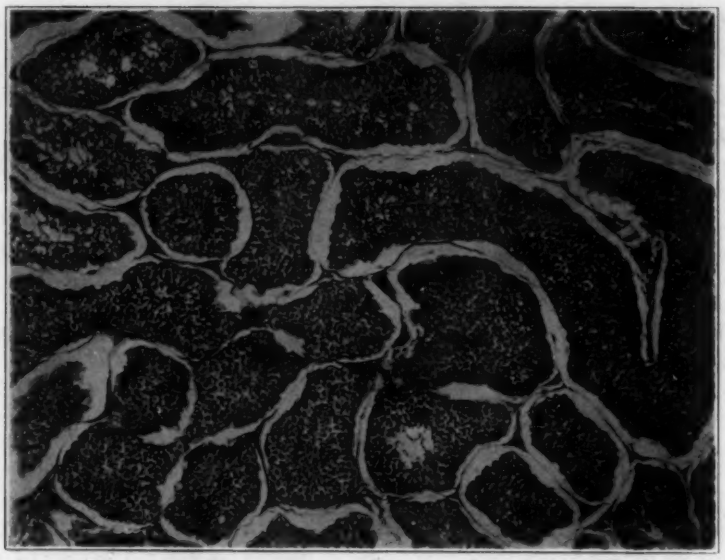

Fig. 1 (experiment 3).—Left testis of adult dog; control in scrotum showing the normal condition in the mature testis in which all the mature germinal cells are present (× 100).

Fig. 2.—Right testis of same dog as shown in figure 1 after having been in the peritoneal cavity for five days; marked destruction of the germinal epithelium; formation of multinucleated cells; Sertoli cells still in fair state of preservation; interstitium normal (× 100).

EXPERIMENT 6.—March, 17, 1925; an adult dog.

Through inguinal incisions the testis was removed from the scrotum on both sides after severing the gubernacula. The spermatic cords were mobilized and both testes were placed in the inguinal region beneath the fat of the abdominal wall.

May 13, fifty-seven days later, castration was done. The left testis had come to be just beneath the skin in a slight outpouching of the skin about 2 inches (5 cm.) distant from the scrotum. The right testis lay beneath the superficial fat. The left testis was larger than the right. The scrotum was shrunken on both sides. The microscopic examination was the same as in dog 5.

Young dogs were used in the following experiments:

EXPERIMENT 7.—Aug. 11, 1923; a pup, aged 4 months.

Both testes were placed in the peritoneal cavity in the usual manner.

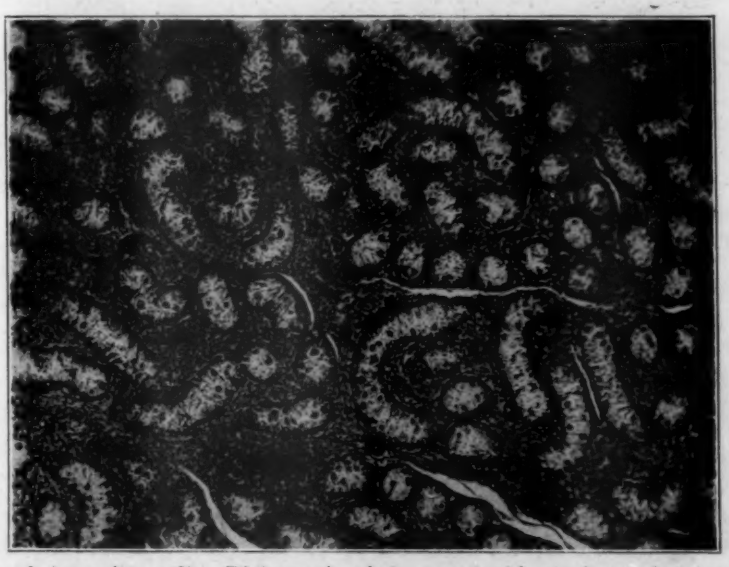

Fig. 3 (experiment 8).—Right testis of dog approaching puberty that has been in the scrotum for ninety-one days; the large mononucleated cells in some of the lumina illustrate the first change noted in the young dog's testis (× 100).

August 18, seven days later, the dog was found dead. A typical normal pup's testis was found. A lumen was established in the tubules. There was definite arrangement of the Sertoli cells at the periphery with only scattered spermatogonia present. There were no giant cells, no débris in the lumina and no evidence of necrobiotic changes in the tubules. There was slight peritubular edema. (Shrinking in fixation may be partially responsible for this appearance.)

EXPERIMENT 8.—Sept. 19, 1923; a small pup, aged 3 months.

The right testis was placed in the peritoneal cavity, and the left testis allowed to remain in the scrotum for control.

December 19, ninety-one days later, the dog, which was mangy, was killed. The right testis was slightly adherent to the parietal peritoneum; the left was free in the scrotum. Both were about the same size.

Microscopically, the testes were those of a normal young pup. There was no elaboration of the germinal epithelium above the spermatogonia. In some of the lumina of the tubules of the right testis, which was placed in the peritoneal cavity, there were large cells with acidophilic cytoplasm. There were no multinucleated cells and no débris in the tubules. (These cells probably represent the earliest degenerative phase in the testes of the young)

EXPERIMENT 9.—Sept. 21, 1923; a small young dog, aged about 3 months.

Both testes were placed in the peritoneal cavity.

November 19, fifty-nine days later, the dog was killed. The left testis was adherent to the abdominal wall; the right was free.

Microscopically, the testis was that of a normal pup. There was no evidence of degenerative phenomena. There were numerous spermatogonia. The germinal epithelium was from two to three rows in thickness. There was no débris in the lumina. Some peritubular edema was noted (shrinking in fixation?).

EXPERIMENT 10.—Sept. 22, 1923; a young dog, aged about 5 months:

Both testes were placed in the peritoneal cavity.

October 5, thirteen days later, the dog was found dead.

Both testes were free in the peritoneal cavity. Microscopically, both these testes showed the picture mentioned in experiment 8, viz., large mononucleated cells with a reddish cytoplasm within the lumina. There were no multinucleated cells and no débris.

EXPERIMENT 11.—Sept. 24, 1923; a 5 months old dog.

Both testes were placed in the peritoneal cavity.

October 5, eleven days later, the dog was killed. The right testis was free in the peritoneal cavity; the left was ensheathed in adhesions of omentum. The epididymis was swollen. The surface of the testis was hemorrhagic. The vessels were slightly twisted.

Microscopically, the right was a normal pup's testis. No degenerative changes were present. The left had many tubules hyaline in appearance. Loss of ability of the cells in the tubules to take a stain was apparent in several areas. There were many polymorphonuclear cells in the interstitium. (This testis apparently was the victim of torsion of its vessels.)

EXPERIMENT 12.—Sept. 29, 1923; a small pup, aged about 4 months.

Both testes were placed in the peritoneal cavity.

December 1, sixty-three days later, the dog died. The right testis was slightly adherent to the greater omentum at the anterior abdominal wall. The left testis was free. There was no torsion of the vessels.

Microscopically, there were large mononucleated cells with acidophilic cytoplasm in the lumina (as in experiments 8 and 10). The outline of the tubules was well preserved. No other degenerative changes were present.

EXPERIMENT 13.—Oct. 11, 1923; a pup, aged 3 months.

Both testes were placed in the peritoneal cavity.

December 19, sixty-nine days later, the dog was killed. Both testes were free in the peritoneal cavity. There was no vessel constriction. The histologic report* was the same as in experiment 12, 8 and 10; that is, there were large

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*Many of these young dogs operated on in the later part of 1923 had mange Though the testis of the young is not as sensitive to the effect of debilitating diseases as is the testis of the adult, nevertheless in the testis immediately before puberty slight degenerative changes are noted. Not unlikely, these are the result of the mange and malnutrition as much as the effect of transplantation. mononucleated cells with the tubule histologically otherwise normal.

EXPERIMENT 14.—Oct. 13, 1923; a small dog, aged 4 months.

Both testes were placed in the peritoneal cavity.

January 24, eighty days later, the dog died.

Microscopically, there was a many layered germinal epithelium in the tubules made up of spermatogonia. In a few tubules the mononucleated cells were present; an occasional multinucleated cell was found in some tubules. No loss of germinal epithelium was apparent. There was no débris in the lumina.

EXPERIMENT 15.—Dec. 23, 1923; a small pup, aged about 4 months.

Both testes were removed from the scrotum and placed beneath the skin in the peritoneum.

Jan. 21, 1924, twenty-five days later, the dog died.

Fig. 4 (experiment 17).—Left testis of young dog; the control in the scrotum shows the normal condition of the young dog's or prepuberty testis (× 100).

Microscopically, a many rowed germinal epithelium was made up of spermatogonia. The contour of the tubules was well preserved. An occasional large mononucleated cell was present in some of the lumina. There was no débris in the lumina.

EXPERIMENT 16.—Feb. 27, 1925; a small dog, aged 3 months.

Both testes were placed in the peritoneal cavity.

March 15, seventeen days later, the dog died. The testes were adherent to one another in the peritoneal cavity.

Microscopically, there was a normal prepuberty testis. No degenerative phenomena were present. The germinal epithelium was from two to three layers in thickness. No adult germinal cells were present.

EXPERIMENT 17.—July 28, 1925; a good sized pup, aged about 5 months.

The right testis was placed in the peritoneal cavity. The left was not touched.

August 17, twenty days later, castration was done. Both testes were of the same size and were microscopically and histologically similar. A many rowed

germinal epithelium was present in both. No degenerative phenomena were present.

EXPERIMENT 18.—July 28, 1925; pup 4, aged 5 months.

The right testis was placed in the peritoneal cavity; the left was allowed to remain in the scrotum.

August 18, twenty-one days later, castration was done. Both testes were the same size. Microscopically, the germinal epithelium was from two to three layers in thickness. Both were histologically alike. No degenerative phenomena were present and no adult germinal cells.

EXPERIMENT 19.—July 31, 1925; a small pup, aged from 2.5 to 3 months.

The right testis was transplanted into the inguinal area; the left was not touched.

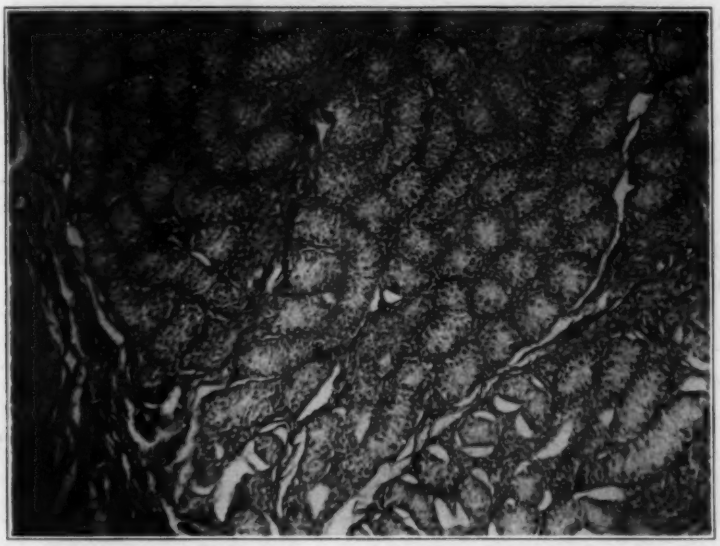

Fig. 5.—Right testis of same dog as shown in figure 4 after having been in the peritoneal cavity for twenty days; the only germinal cells present in either section are the spermatogonia; there is no appreciable histologic difference (× 100).

August 27, twenty-seven days later, castration was done. Both testes were the same size. Microscopically, a many layered germinal epithelium was present. No degenerative phenomena were observed. Histologically they were similar.

EXPERIMENT 20.—July 31, 1925; a small pup, aged 6 weeks.

The right testis was transplanted into the inguinal region; the left was not touched.

August 27, twenty-seven days later, castration was done. Both testes were of the same size. Microscopically, the central lumen was not established. There was a single layered germinal epithelium. The interstitium was prominent. Both were alike, and no degenerative changes were present.

The transplanted testis when removed, after a few days in its new environment, though appearing grossly much the same as its fellow in the dog's scrotum, microscopically shows a marked degeneration of the

germinal epithelium. This dissolution of the cellular elements constituting the walls of the seminiferous tubules is most striking. Heaped up in the lumina of the tubules is a cellular débris surrounded by an irregular and much thinned and scarcely recognizable germinal epithelium. In the lumina of many of these tubules are multinucleated or giant cells. The interstitium is not affected. After from two to three weeks have intervened following removal of the testis from the scrotum, the germinal epithelium has almost disappeared. Only here and there a few spermatogonia persist in the seminiferous tubules beside the Sertoli cells. The débris in the lumina disappears and after a few months absence from the scrotum the seminiferous tubules have the appearance of vacuolated rings with a single layer of cells constituted by the Sertoli cells.

The spermatogonia are the most resistant of the germinal cells and are the last to disappear. Maximow,[180] who has studied in an exhaustive treatise the histologic changes that occur in the testis after injury, states that the spermatogonia do not participate in the giant cell formation. The removal of the necrotic masses and giant cells from the lumina he ascribes to the phagocytic action of the Sertoli cells and connective tissue phagocytes and to dissolution and removal through the epididymis.

In the young dogs' testes in which spermatogenesis had not occurred none of these histologic changes were observed. No difference was noted between the control organ in the scrotum and the testis deposited in the abdominal cavity or inguinal region, in young pups from 2 to 3 months of age. However, in a few young dogs from 4 to 6 months of age, in whom spermatogenesis had not yet been established, a few large cells with acidophilic cytoplasm were found in the lumina of the tubules. In these dogs the spermatogonia are probably in preparation to elaborate the more mature germinal cells, and have just begun to exhibit the sensitivity that is so apparent after spermatogenesis has supervened.

The spermatogonia are the most resistant of the germinal cells and are the last to disappear. But that they do disappear is evident from microscopic examination of the testes that have long been removed from the scrotum. Spermatozoa were found in the epididymis by fresh smear in many of the dogs that were castrated a few days after the original procedure. This is in agreement with the finding of sperm in the ejaculations of persons who have recently been castrated. Impregnation of the ovum usually occurs in the fallopian tube, so that the spermatazoon apparently is immune to the changes that befall the other germinal cells when the testis is removed from the scrotum. The spermatocytes are the most vulnerable and these Maximow [180] says contribute largely to the formation of the giant cells. After the removal of the products of

necrobiosis from the lumina only the Sertoli cells remain within the tubules. Many of these have altered nuclei with only a scant amount of chromatin and lie on the membrana propria of the seminiferous tubules as empty irregular sacs.

None of these degenerative changes were observed in the interstitium. On the contrary, the interstitial cells appear prominent and increased in number. An actual hyperplasia seems to have occurred. Oslund [203] believes, however, that this increase is probably relative because of the disappearance of the germinal epithelium.

Fig. 6 (experiment 21).—Right testis of adult dog mobilized as for transplantation into the peritoneal cavity but immediately redeposited in the scrotum; removed twenty-five days later; the damage incident to the manipulation is apparent (× 100).

## EXPERIMENTS TO DETERMINE THE REACTION OF THE TESTIS TO INJURY

### SERIES II

EXPERIMENT 21.—Aug. 4, 1923; an adult dog.

Both testes were freed from the scrotum and prepared as for transplantation into the peritoneal cavity, but were immediately replaced in the scrotum.

August 29, twenty-five days later, the dog died without apparent cause. The wounds were well healed. The testes were slightly smaller than at operation. Microscopically, there was marked destruction of the germinal epithelium, most of which had disappeared. A few spermatogonia still remained. In the lumina of the tubules numerous giant cells and débris were present. In many tubules the

products of necrobiosis had been removed. The picture was similar to actual transplantation of the testis.

EXPERIMENT 22.—Aug. 22, 1923; a large pup, aged about 5 months.

Both testes were loosened up as in abdominal reposition; the left gubernaculum was not cut; the right was severed and the testis and cord were mobilized. Both testes were left in the scrotum.

September 6, fifteen days later, the dog died. There was a small stitch abscess in the left wound. Microscopically, the picture was that of a pup's testis. A two rowed germinal epithelium was present. No degenerative phenomena were noted.

EXPERIMENT 23.—Dec. 19, 1923; an adult dog.

Both testes were mobilized as for transplantation into the peritoneal cavity but were replaced in the scrotum immediately. The tunica vaginalis testis was removed on the right but left intact on the left.

Feb. 29, 1924, seventy-two days later, castration was done. The testes were normal microscopically. All the adult germinal cells including spermatozoa were present. The tunica vaginalis testis was removed on the right, without consequence.

EXPERIMENT 24.—Dec. 20, 1923; an adult dog.

Both testes were mobilized well into the retroperitoneal space and were replaced in the scrotum immediately.

January 19, thirty days later, the dog was castrated. Microscopically, there were numerous areas in which the germinal epithelium had almost disappeared. In a few tubules numerous spermatogonia were still present. An occasional giant cell was present in some of the tubules. (In this section apparently, the injury had occurred; the destructive process was about at an end and the regenerative changes were beginning.)

EXPERIMENT 25.—Dec. 20, 1923; an adult dog.

The testes and spermatic cord in both sides were well mobilized to the peritoneum; the testes were allowed to remain in the scrotum.

December 26, castration was done. Six days later microscopically the condition was the same as after transplantation in a six day testis, though less uniform and of a milder degree. In areas the destructive process was not much in evidence; in other areas practically all the germinal epithelium had disappeared and only giant cells and débris occupied the lumina of the tubules.

When the adult dog's testis is loosened from the scrotum and perpared as for abdominal reposition but replaced immediately in the scrotum, the same changes are observed within the lapse of a few days as occur in the case when testes are actually placed in the peritoneal cavity, though in slighter degree. The disappearance of the germinal epithelium is not so uniform but the giant cells are present and the lumina are filled with the débris of the germinal cells in the process of dissolution. Considerable peritubular edema also is present. This is the reaction of the young testis to trauma. No dissolution of the epithelial cells within the lumina is noted in young testes. In the testes of the new-born, this peritubular edema and even hemorrhage into the intertubular spaces are well known.

## TRANSFERENCE OF THE TESTIS TO THE PERITONEAL CAVITY OR INGUINAL REGION WITH REPLACEMENT IN THE SCROTUM AT A LATER DATE, WHEN DEGENERATIVE CHANGES HAVE OCCURRED IN THE TRANSPLANTED ORGAN

### SERIES III

EXPERIMENT 26.—July 8, 1923; an adult dog.

Both testes were transplanted into the inguinal region.

August 20, forty-two days later, the right testis was redeposited in the scrotum. The left testis was removed.

October 29, seventy-one days later, the right testis was removed. Microscopically, the left testis showed a typical transplant testis in which the germinal epithelium had practically disappeared. The products of necrobiosis had been

Fig. 7 (experiment 27).—Right testis of dog after having been in the peritoneal cavity for thirty-seven days (× 100).

removed. In the right testis definite attempt had been made to regenerate the germinal epithelium. In areas all the adult sex cells were present, including a few spermatozoa.

In those tubules in which the spermatogonia had all disappeared, no regeneration was apparent.

EXPERIMENT 27.—Feb. 18, 1925; a large adult bulldog.

Both testes were placed in the peritoneal cavity.

March 27, thirty-seven days later, the right testis was removed. The left testis was replaced in the scrotum. The spermatic cord was not under tension. The testis was sutured to the bottom of the scrotum, and the tunica vaginalis testis covering the testis was included in the sutures that united the inner layer of the scrotum.

November 4, 190 days later, the left testis, which was of good size, was removed. It was movable in the scrotum. Microscopically, the right testis was a

typical transplant testis. Nearly all the germinal epithelium had disappeared. A few spermatogonia still persisted in most tubules. The necrotic elements had been removed.

In the left testis the regeneration that had occurred was remarkable. Practically every tubule had the normal condition reestablished with all the mature germinal cells present, including numerous spermatozoa.

EXPERIMENT 28.—March 3, 1925; an adult dog.

Both testes were transplanted into the inguinal region.

April 6, thirty-four days later, the left testis was removed and the right testis was replaced in the scrotum.

August 19, 135 days later, the right testis, which was of good size, was freely movable in the scrotum. Microscopically, there was marked degeneration of the germinal epithelium in the left testis. In the right elaboration of all the mature

Fig. 8.—Left testis of same dog as shown in figure 7, also in the peritoneal cavity for thirty-seven days but replaced in the scrotum and removed 190 days later (× 100).

germinal cells in most of the tubules had occurred. Here and there was a vacant tubule. Spermatozoa were present in abundance.

EXPERIMENT 29.—March 6, 1925; an adult dog.

Both testes were disclosed into the inguinal region after the gubernacula were severed.

April 16, 101 days later, the left testis was removed and the right testis was replaced in the scrotum.

September 29, forty-two days later, the right testis was not in the scrotal pouch but was at the lower end of the inguinal canal. The right testis was removed.

Microscopically, the left testis was the picture of atrophy following transplantation. A few spermatogonia persisted. The atrophy was more complete in the right than in the left testis. No germinal cells remained.

EXPERIMENT 30.—Aug. 4, 1925; an adult dog.

Both testes were transplanted into the inguinal region.

August 18, fourteen days later, the left testis was removed and the right was replaced in the scrotum.

November 4, seventy-eight days later, the right testis was removed. It was high in the scrotum but movable. Microscopically, the left was degenerate with most of the germinal epithelium gone. There was elaboration of all the mature germinal cells in many tubules of the right. Quite a number of tubules, however, were vacant. There was no evidence of degenerative changes. (Lack of regeneration in many tubules were probably due to the high scrotal position of the testis.)

EXPERIMENT 31.—Aug. 19, 1925; an adult dog (old).

Both testes were transplanted into the inguinal areas.

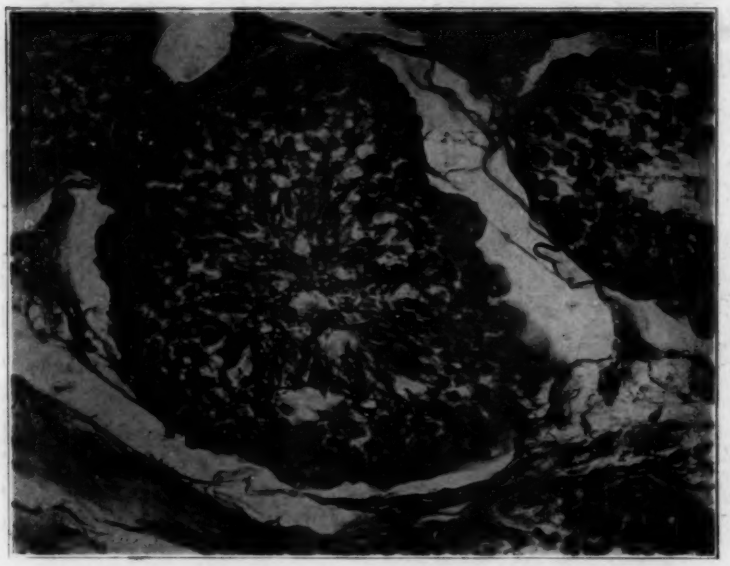

Fig. 9.—Same testis as shown in figure 8, under high power; figures 8 and 9 illustrate well the regeneration that occurs with replacement of the testis in the scrotum; all the mature germinal cells are present, and spermatozoa in abundance (× 250).

August 29, ten days later, the right testis was removed and the left was returned to the scrotum.

November 4, sixty-seven days later, the left testis was removed. The testis was movable in the scrotum. The degenerative phenomena were marked in the right testis and were still in progress. Giant cells and débris filled the lumina of most of the tubules. Regenerative phenomena were present in almost every tubule in the left testis. The germinal epithelium consisted largely of spermatogonia and spermatocytes. A few spermatids and spermatozoa were present.

EXPERIMENT 32.—Aug. 20, 1925; a large adult dog.

Both testes were transplanted into the inguinal areas.

September 2, thirteen days later, the left testis was removed and the right was replaced in the scrotum.

November 4, sixty-three days later, the right testis was removed. It was a large testis, freely movable in the scrotum. The left was a degenerate testis with necrobiosis still in progress. Giant cells were present in almost every tubule. Regenerative phenomena were quite uniform in the right. There was elaboration of all the mature germinal cells, including the spermatozoa.

EXPERIMENT 33.—Aug. 20, 1925; a large adult dog.

Both testes were transplanted into the inguinal region.

September 2, thirteen days later, the right testis was replaced in the scrotum. The left was removed.

December 15, 104 days later, the right testis was removed.

Microscopically, the left testis gave about the same histologic picture as the dog in experiment 32. Most of the germinal epithelial cells had disappeared.

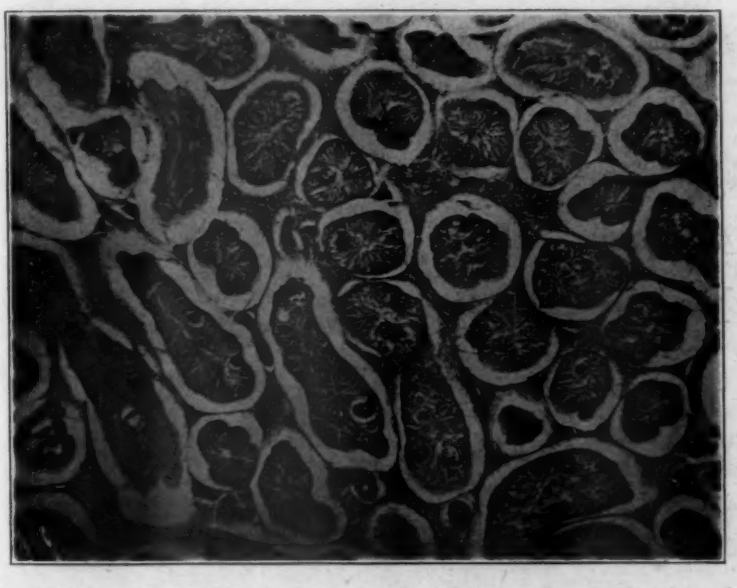

Fig. 10 (experiment 32).—Left testis of adult dog after having been in the inguinal region for thirteen days; the giant cells and débris have not yet been removed from the tubules.

Numerous giant cells were present. The normal condition had been reestablished in most of the tubules of the right. All the adult germinal cells, including spermatozoa, were present in abundance.

EXPERIMENT 34.—Aug. 21, 1925; a large mature dog.

Both testes were transplanted into the inguinal area.

September 4, fifteen days later, both testes were replaced in the scrotum.

December 15, 102 days later, both testes were removed. The scrotum was pendant on both sides; the testes were movable in the scrotum. Both testes were of good size.

Microscopically, both testes showed the normal adult condition present in nearly all the tubules.

EXPERIMENT 35.—Aug. 21, 1925; a large adult dog.

Both testes were transplanted into the inguinal area on each side.

September 10, twenty-one days later, the left testis was removed; the right testis was replaced in the scrotum.

December 15, ninety-six days later, the right testis was removed; a large testis was movable in a pendant scrotum.

Microscopically there was almost complete disappearance of most of the germinal cells in the left testis. Only a few spermatogonia remained. In the right the normal condition had been reestablished in most of the tubules. In some there were no adult germinal cells.

EXPERIMENT 36.—Sept. 1, 1925; a medium sized adult dog.

The right testis was transplanted into the inguinal area. The left testis was allowed to remain in the scrotum.

September 17, sixteen days later, the right testis was replaced in the scrotum.

Fig. 11 (experiment 32).—Right testis of same dog as shown in figure 10, also in the inguinal region for thirteen days but replaced in the scrotum (when the left testis was removed) and allowed to remain in the scrotum for sixty-three days. Regeneration in a much shorter time is possible when the testis does not remain too long outside the scrotum.

December 18, ninety-two days later, both testes were removed. The testes were about of the same size, movable in the pendant scrotum.

Microscopically, the left was normal and there was elaboration of all the adult germinal cells in nearly all the tubules of the right.

EXPERIMENT 37.—Sept. 3, 1925; a large adult dog.

The right testis was transplanted into the inguinal region. The left was not touched.

September 16, thirteen days later, the right testis was replaced in the scrotum.

December 18, ninety-three days later, both testes were removed. The left was somewhat larger than the right.

Microscopically, the left was normal; marked regeneration was noted in most of the tubules of the right. A few showed little or no regeneration.

The testes of several mature dogs were transferred to the peritoneal cavity and inguinal region. After the lapse of a period of time, one testis was removed to determine the amount of injury and the other was replaced in the scrotum. These were subsequently removed and comparisons with the control organ made to determine whether regeneration of the germinal epithelium in the seminiferous tubules had occurred. In every instance but two marked regeneration of the germinal epithelium with formation of spermatozoa had occurred. The photomicrographs of the controls and the testis replaced in the scrotum illustrate well the ability of the germinal epithelium to be regenerated if the testis is redeposited in the scrotum. When the testis remains too long in the peritoneal cavity and most of the spermatogonia are destroyed the regenerative ability of the germinal epithelium is lost. This occurred in the fourth dog in this series. After remaining for 101 days in the peritoneal cavity, this testis was replaced in the scrotum. No evidence of regeneration was apparent after forty-two days. In the fifth dog in this series the testis had retracted out of the scrotal pouch and was found at the lower end of the inguinal canal. The physiologic position of the testis at the bottom of the scrotum must therefore be restored. In all these scrotal repositions, the testis was sutured to the bottom of the scrotum. The purse string suture used at the upper end of the scrotum prevents retraction out of the scrotal pouch, but this is not the proper location of the testis. This point will be discussed at greater length when the surgery of undescended testes is considered.

## LIGATION OF THE VAS DEFERENS

### SERIES IV

Ligation of the vas deferens was carried out on one side, and on the other all the vessels to the testis including the vessels accompanying the vas deferens were severed. Only the vas itself remained intact on this side.

EXPERIMENT 38.—Aug. 23, 1923; a pup, aged about 5 months.

The right vas deferens alone was ligated and severed on the left. All the vessels were cut and tied; only the vas itself was left intact.

September 7, fifteen days later, castration was done. There was only a small piece of scar tissue on the left. The right testis was of the same size as at the original procedure. Microscopically, the right showed a prepuberty testis in which no germinal cells beyond the spermatogonia had been formed. There were no degenerative changes. In the left only fibrous connective tissue remained.

EXPERIMENT 29.—Aug. 24, 1923; a large young dog.

The right vas deferens only was ligated and severed. On the left all the vessels to the testis and epididymis were severed and doubly ligated.

December 27, 125 days later, castration was done. Measurements of the right testis showed that it had increased in size since the previous procedure (to 4 by 3 by 2.5 cm. from the previous 3 by 2.3 by 2 cm.). Microscopically, in the right all the mature germinal cells were present, including spermatozoa. No sections were made of the left.

EXPERIMENT 40.—Aug. 27, 1923; a large mature dog.

The right vas deferens was ligated and severed. On the left all vessels were cut, leaving only the vas deferens intact.

December 20, 115 days later, castration was done. Only a small piece of scar tissue was noted on the left. The right testis was of good size. Microscopically, it was a normal testis with spermatozoa present in abundance. Only fibrous connective tissue remains in the left. Occasionally there was a suggestion of the outline of a previous tubule.

EXPERIMENT 41.—Sept. 4, 1923; a large adult dog.

The right vas deferens was ligated and severed. On the left only the vas deferens itself was allowed to remain intact.

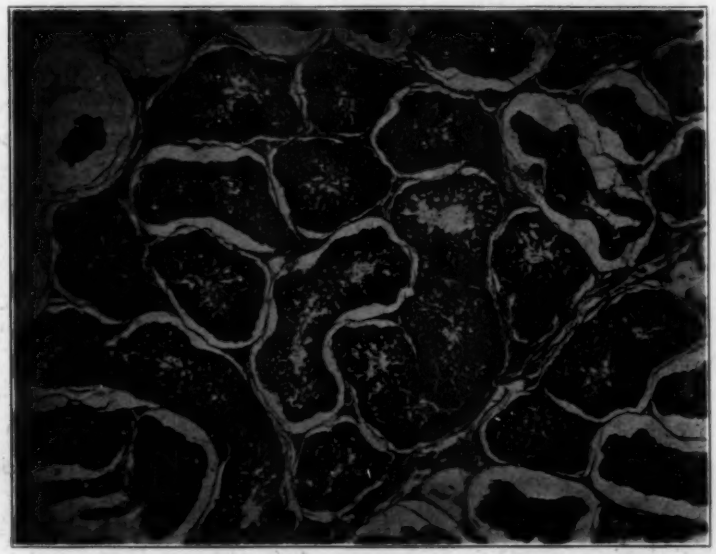

Fig. 12 (experiment 40).—Right testis of dog, 115 days after ligation of the vas deferens; the normal condition is present.

December 28, 15 days later, castration was done. There was only scar tissue on the left but a large testis on the right. Microscopically, the right was a normal testis. All the mature germinal cells and spermatozoa were present in all the tubules. No sections were made of the left.

EXPERIMENT 42.—Sept. 6, 1923; a large mature dog.

The right vas deferens was cut and ligated. On the left only the vas deferens itself was allowed to stay intact. All vessels were severed and doubly ligated.

September 24, eighteen days later, the dog died. There were gangrene and sloughing of the left testis. The right wound healed. Microscopically, on the right degenerative phenomena were present as observed in manipulation of the testis alone. No sections were made of the left testis.

EXPERIMENT 43.—Sept. 7, 1923; a large dog, aged 5 or 6 months.

The right vas deferens was doubly ligated and severed. On the left all the vessels were cut; only the vas deferens was left intact.

December 20, 102 days later, castration was done. The right testis had increased in size since the previous operation (from the previous 2 by 1.2 by 0.8 cm. to 3 by 2 by 1.5). Only a small piece of scar tissue was present on the left.

Microscopically, all the adult germinal cells except spermatozoa were in evidence. Numerous spermatocytes and spermatids were present. No sections of the left were made.

In these experiments no appreciable change was observed to occur in the testis following severance of continuity of the vas deferens when sufficient time was allowed to intervene before the dogs were castrated, to preclude damage attendant on the original operative procedure. Spermatogenesis continued despite the interruption of the excretory duct of the gland. No hyperplasia or hypertrophy of the interstitial cells was observed.

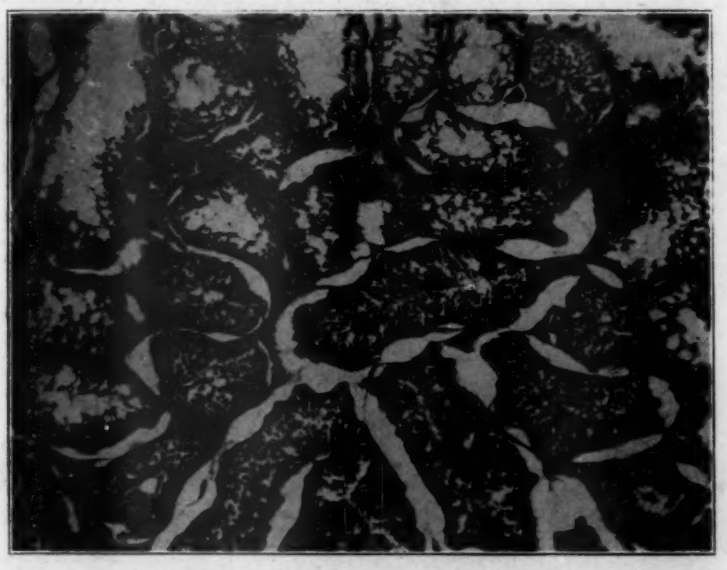

Fig. 13 (experiment 50).—Left testis of dog, 117 days after ligation of internal spermatic artery and anterior group of veins in the pampiniform plexus; the testis was much reduced in size, but the mature germinal cells were present. Ligation of the internal spermatic artery alone produces about the same picture.

### BLOOD VESSEL LIGATIONS

#### SERIES V

EXPERIMENT 44.—Sept. 10, 1923; a large mature dog.

The internal spermatic artery and veins in the pampiniform plexus were severed and ligated on both sides leaving the vas deferens and its accompanying vessels intact.

December 28, 109 days later, castration was done. The dog had gained markedly in weight. The testes were small. Microscopically, no seminiferous tubules were recognizable. There was fibrous connective tissue replacement of the entire gland; numerous areas of pigment deposit were noted; the interstitium also was destroyed.

EXPERIMENT 45.—Sept. 11, 1923; a large mature dog.

The same procedure was used as in experiment 44.

December 28, 108 days later, the testes were small. The dog had increased in weight. Microscopically, the picture was the same as in experiment 44. The epididymis was normal. Only fibrous tissue and deposits of a brownish pigment persisted in the testis.

EXPERIMENT 46.—Sept. 17, 1923; an adult dog.

The vessels on both sides were ligated and severed, leaving the vas deferens and its accompanying vessels intact.

October 5, eighteen days later, both testes were large and injected. Microscopically, the contour of the tubules was still preserved. The lumina of the tubules was occupied by red blood cells. Most of the germinal cells had disappeared. There was marked edema in the interstitium. Most of the cells stained poorly.

EXPERIMENT 47.—Dec. 27, 1923; an adult dog.

The internal spermatic artery was ligated on both sides.

Fig. 14 (experiment 45).—Right testis of adult dog in which the internal spermatic artery and all the veins were ligated, leaving only the vessels accompanying the vas deferens intact; testis removed 108 days later; the parenchyma of the gland and interstitium as well were destroyed; only fibrous connective tissue remained.

Feb. 29, 1924, sixty-four days later, castration was done. Both testes were reduced in size. The microscopic section showed a fairly normal testis with all the mature germinal cells present. Only a few tubules at the periphery exhibited degenerative phenomena.

EXPERIMENT 48.—March 3, 1925; a large adult dog.

The left testis and spermatic cord were not touched. On the right the internal spermatic artery and anterior vein in the pampiniform plexus were cut and ligated, leaving the posterior vein and the vas deferens and the vessels accompanying it intact.

June 9, ninety-eight days later, castration was done. The left testis was about twice as large as the right. Microscopically the left was normal. On the right

there was a large area of fibrosis in the midportion of the testis. Most of the tubules showed normal spermatogenesis with spermatozoa present.

EXPERIMENT 49.—March 17, 1925; a large mature dog.

The internal spermatic artery was ligated and severed on both sides.

June 9, eighty-four days later, castration was done. Both testes were smaller than at the original procedure. Microscopically there was fibrosis in these areas. Spermatocytes and spermatids were present but no spermatozoa (a well elaborated germinal epithelium, however, which could develop normal spermatogenesis).

EXPERIMENT 50.—March 25, 1925; a large adult dog.

On the right the internal spermatic artery was ligated and severed. On the left the internal spermatic artery and anterior vein in the pampiniform plexus were ligated, leaving the posterior vein intact, as well as the vas deferens and its accompanying vessels.

Fig. 15.—The testis of a boy of 19 who, six years previously, had an orchidopexy performed in which all the vessels, except those accompanying the vas, were divided, in order to place the testis in the scrotum; the similarity to figure 14 is apparent.

July 20, 117 days later, castration was done. Both testes were smaller. Microscopically, both appeared much alike. Spermatogenesis was present in most tubules. A few were empty. Numerous spermatozoa were present.

EXPERIMENT 51.—April 9, 1925; a mature dog.

On the right the veins in the pampiniform plexus only were ligated and severed. The internal spermatic artery and the vas deferens and its vessels were left intact. On the left the internal spermatic artery and the anterior vein in the pampiniform plexus were ligated, leaving the posterior vein and the vas deferens and its vessels intact.

July 20, 102 days later, castration was done. Both testes were smaller. On the right a fairly well differentiated germinal epithelium was present. There

were no spermatozoa. In many tubules at the periphery most of the cells had disappeared. (Separation of the vessels in the pampiniform plexus is always difficult because of the small size of the vessels. In all these experiments the internal spermatic artery, when cut, was allowed to spurt to be certain that the artery had really been severed. In the veins the procedure is not quite so simple. From what has happened in ligation of the internal spermatic artery alone and then ligation of the artery with one vein, and ligation of all the vessels save those accompanying the vas deferens, it is observed that only the latter procedure produces a complete degeneration. Separation of the vessels is attended with even greater difficulty just above the testis.) The left was fairly normal. There was elaboration of all the mature germinal cells. A few atrophic tubules were noted at the periphery.

Fig. 16.—Testis of a man of 22; three years previously this testis was high in the inguinal region; in order to place it in the scrotum, all the vessels except those accompanying the vas deferens were severed; the bare outline of a few tubules still persists.

Experiment 52.—Sept. 16, 1925; a large adult dog.

The internal spermatic artery and the anterior vein in the pampiniform were severed and ligated leaving the posterior vein intact on the right. On the left both veins in the pampiniform plexus were severed and ligated, leaving the internal spermatic artery intact. On both sides the vessels accompanying the vas deferens were not disturbed. The vessels in each instance were exposed in the upper portion of the inguinal canal.

December 15, ninety days later, both testes were removed. The right testis was considerably reduced in size. The left testis was about normal size.

Microscopically, on the right there were areas of fibrosis, especially at the periphery. Elaboration of most of the adult germinal cells in the remaining tubules was noted. The normal condition was present in most tubules of the left.

Invariably after ligation of all the vessels in the spermatic cord except the artery to the vas deferens, complete atrophy of the germinal epithelium and interstitium occur such that the parenchyma of the gland is replaced by fibrous tissue. The epididymis continues normal. In the animals in which castration was done after a shorter interval, necrosis of the parenchyma of the testis was observed. After ligation of the internal spermatic artery, a diminution in size of the testis is constantly noted. Many of these testes, however, appear fairly normal throughout the greater portion of the gland on microscopic examination. Here and there at the periphery atrophic tubules occur. A lesser number showed this partial degenerative process fairly well disseminated throughout the greater portion of the gland. Ligation of the internal spermatic artery with either the anterior or posterior group of veins in the pampiniform plexus leads to a rather more marked degenerative process than does ligation of the artery alone. When interruption of all the blood supply to the testis occurs, that is, ligation of the internal spermatic artery and veins in the pampiniform plexus together with the vessels accompanying the vas deferens, the testis shrinks up to a mere nubbin of scar tissue. Gangrene was observed only once and in this instance infection was present.

### EXAMINATION OF UNDESCENDED TESTES IN MAN

#### SERIES VI

Seventeen testes that had failed to reach the scrotum were obtained for examination. Unfortunately no prepuberty undescended testes were available. In the testes of old subjects, even the seminiferous tubules had a hyaline appearance. The interstitial cells appeared increased in number. In two testes spermatogonia were observed. In the testis of a boy of 17 spermatocytes also were present. The similarity between the undescended testis in man and the experimentally ectopic testis of the dog is apparent.

### THE TESTIS IN LARGE SCROTAL HERNIAS AND HYDROCELES

#### SERIES VII

Nine testes that were removed in the cure of large old scrotal hernias were examined. Fourteen testes were obtained for examination from patients who had had large hydroceles over a long period of time (8-12 ounces [236 to 355 cc.] of fluid present) and six were examined in whom both a scrotal hernia and a hydrocele had existed together.

As long as the testis continues in the scrotum, the elaboration of the adult germinal cells is possible. In the testes of men in whom large scrotal hernias or hydroceles had been present for years, the normal condition prevailed. The only anatomic peculiarity observed was an apparent increase in size of the lumen with a tendency to the formation

of diverticula and a thinning of the germinal epithelium. As all these testes were from men of advanced years, this finding is compatible with what has been described as the normal condition in old men.[253] In two men of 81, spermatozoa were observed. It is said that spermatogenesis disappears in the senile testis.[111]

### EXAMINATION OF TESTES OF MEN DYING OF ACUTE AND CHRONIC FEBRILE DISEASES

#### SERIES VIII

Thirty-five testes were examined in this series. A scattered disappearance of the germinal epithelium appears in a number of testes of

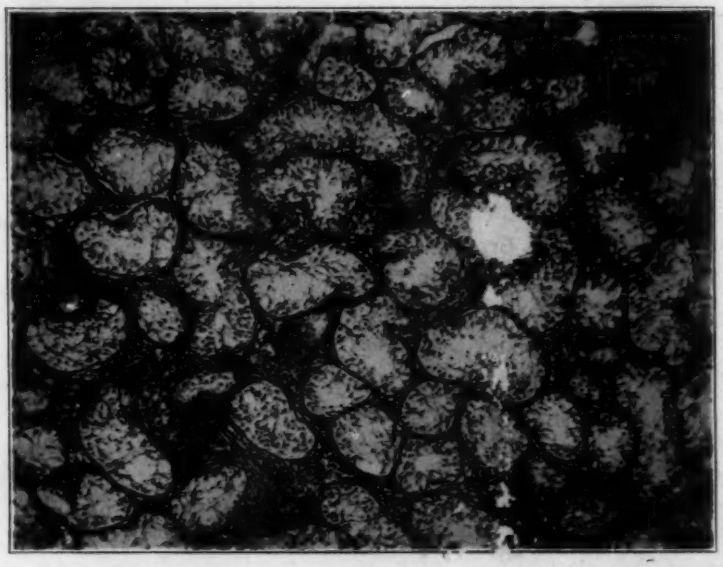

Fig. 17.—Inguinal testis of a boy of 17, removed during the course of a hernia operation; spermatogonia are in evidence; the more mature germinal cells, however, are absent; comparison should be made with a transplant testis.

persons dying of acute and chronic diseases. In a few the testis preserves the normal condition. The more uniform finding, however, appears to be a mild degenerative process in which the mature germinal cells disappear. Disappearance of the spermatogonia rarely occurs so that the normal condition may be quickly reestablished after the removal of the toxic agent.

### COMMENT

The histologic change that occurs in the adult testis with removal from the scrotum has long been known. In 1891 Piana * interfered

* Piana: La Clinica Veterinaria, 1891, quoted by Stilling.[289]

with the descent of the testis in white rats and observed a marked atrophy of the germinal epithelium. Griffiths [112] in 1892 was the first to observe this change in dogs. He also noted the difference in reaction to abdominal transference of the testis in young and old dogs. In 1894 Stilling [260] placed the testes of twenty rabbits in the peritoneal cavity by severing the gubernaculum without even closing the internal ring; atrophy occurred in every instance. In 1905 Matsuoka [178] transplanted the testes of seven rabbits into the abdominal wall. At a subsequent date he cut the vessels and the vas deferens; a necrosis of the testis resulted. Schmidt [235] in 1913 confirmed Griffiths' [112] previous observa-

Fig. 18.—Inguinal testis of a man of 56 removed during the course of a hernia operation; no germinal epithelium is present; only a few Sertoli cells remain; the interstitium is normal.

tions. More recently Moore,[189, 190, 191] Fukui [102, 103, 104] and Fukiyiro [101] have noted the same effect.

Piana concluded from his experiments that the temperature in the abdomen was unfavorable for the testis.[260] Griffiths [112] could give no accurate answer as to the cause of the atrophy, but thought that the removal of the cremaster was responsible. Stilling [260] postulated that kinks in the epididymis were causative. Schmidt [235] believed that the lack of fixation of the testis transplanted into the abdomen and the abdominal pressure were responsible for its atrophy. Both Moore [190, 191, 193] and Fukui [103, 104] believe that the thermal factor is responsible for the degenerate condition of the testis removed from the scrotum.

Removal of the tunica vaginalis testis is only of transitory consequence. Alessandri,[4] Rolando,[224] Martini * and Schmidt [235] have made the same observation. Where removal of the tunica vaginalis alone has been done, the temporary degeneration that occurs is due to the manipulation, not to the deprivation from the testis of its superficial covering. Hanoaka [120] has shown that the tunica albuginea may also with impunity be removed. Only a few tubules at the periphery degenerate permanently.

Interference with the nerve supply of the testis has also been said to bring about degenerative changes in the testis. Kuntz [150, 151] and Takahashi [262, 263] have investigated this assertion of Obolensky [200] and have observed the same result. They believe that the sympathetic nerve exerts a trophic action on the testis. Lipschütz and Voss [168] in similar experiments on cats failed to observe atrophy in a single instance. Certainly in none of the above mentioned cases in which atrophy was observed was the factor of trauma satisfactorily eliminated.

The effect of ligation of the vas deferens on the testis is still a disputed matter. The Steinach theory of rejuvenation is founded [258] on the idea that atrophy of the germinal epithelium and hypertrophy of the interstitial cells follow occlusion of the vas deferens. Cooper [54] in 1823 ligated the vas deferens of a dog and six years later observed spermatozoa in the corresponding testis. Curling,[64] Gosselin [109] and Godard [106] were of the same opinion. Brissaud [32] failed to observe any histologic change in the testis following vas ligation, but postulated that this procedure put the testis in a resting state. Griffith [115] stated that vas ligation was without effect. Bouin and Ancel [27] in 1903 ligated the vas deferens in guinea-pigs and observed atrophy. At this time they suggested that the interstitial cells, which previously had been considered by most investigators as a trophic organ,[211] were responsible for the internal secretion of the testis. In young guinea-pigs they failed to observe the degeneration noted in the older animals. Recently they have repeated their earlier experiments on dogs [6] and obtained the same degenerative changes. Kuntz,[151] Van Wagenen [280] and Sand [229, 230] also find that occlusion of the vas deferens is followed by atrophy of the germinal epithelium. Fukui [104] states that vas ligation causes a degenerate testis. Martini † ligated and resected the epididymis at the caput, Steinach's site of election, but failed to produce other than a temporary atrophy of the germinal epithelium. Tiedje,[269] Retterer and Voronoff [221] find that the disappearance of the germinal cells is only transitory. Wheelon [291] failed to observe atrophy following vas ligation. Oslund [202] and Moore and Quick [192] state that no atrophy occurs following ligation

* Martini: Ztschr. f. Urol. 1908, pp. 728-745.

† Martini: Ztschr. f. Urol. 1908, pp. 728-745.

of the vas deferens. Oslund [202] calls attention to the fact that the testis must be known to be in the scrotum. In many cases, the ligation has been practiced on rodents in which the testes may be retracted out of the scrotum at will. Oslund [202, 203] and Moore and Quick [192] have not observed hypertrophy of the interstitial cells following vas ligations. In the experiments done by me the germinal epithelium did not disappear, nor was hypertrophy of the interstitium noted. When the testis is known to be in the scrotum and a sufficient length of time intervenes to preclude damage as a result of operative trauma, ligation of the vas deferens should be without event in normal healthy animals. Certainly

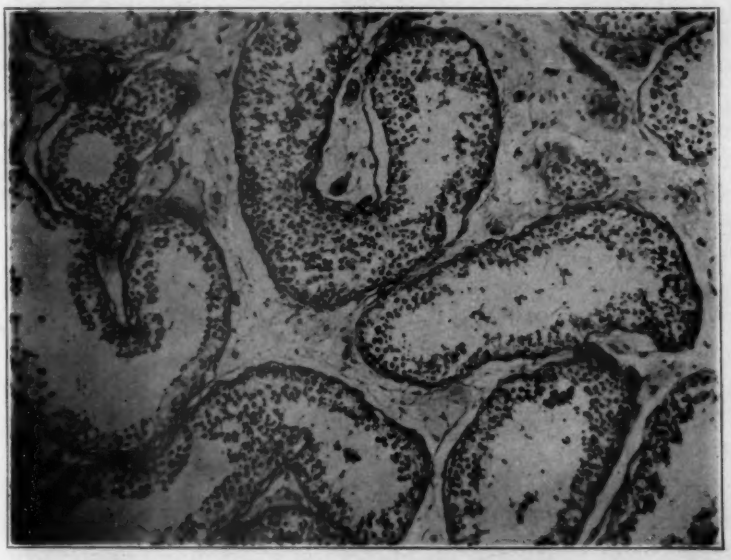

Fig. 19.—Scrotal testis of a man of 81 who had a large scrotal hernia and hydrocele for many years; the normal condition is present; the lumina appear unusually large and diverticula in the tubules are present—both normal findings in the testis of the aged.

any kinks that may occur in the vas deferens or epididymis when the testis is not in the scrotum is not the cause of the atrophy.

The rejuvenation of senile animals noted by Steinach [258] following this procedure is difficult to account for. In the results obtained by Steinach [258] and Sand [230] in patients the psychic effect or reaction to the operation may in a large measure discount the credit due the procedure. Certainly no histologic effect follows interruption of the vas in man or animals. In congenital absence of the vas deferens and after a number of years occlusion following gonorrheal epididymitis, the histology of the seminiferous tubules and interstitium still remain normal.[140]

Walker [285] and Fukui [104] have recently stated that the internal secretion arises in the spermatogenous elements. Though the internal secretion has not been definitely shown to take origin in the cells of Leydig, the weight of evidence would point toward these as its source.[118, 119] In cryptorchids in whom the secondary sex characters are preserved there is no germinal epithelium. Many of the Sertoli cells are in a degenerate state. Though the Sertoli cell cannot be ruled out of consideration as can the germinal cells, the available evidence would indicate that the interstitial cell is responsible for the internal secretion of the testis.

The difficulty of preserving as a graft so highly specialized a tissue as a testis is apparent. When all the vessels to the testis are ligated, a mere nubbin of scar tissue results. In such an experiment, an autograft is really created. Certainly the circumstances for a good result should be more favorable here than in a homo or hetero transplant. Lichtenstern [165] states that undoubtedly good results are obtained by homotransplantation of testicular grafts. Retterer's and Voronoff's [222] histologic studies of their own experiments on animals, however, would indicate the contrary.

In 1889 Brown-Sequard [36] demonstrated the efficacy of subcutaneous injections of testicular extract. Recently these results have been confirmed.[255] The administration of the active principle of the internal secretion of the testis by the hypodermic needle would appear to be more rational than the two procedures practiced today.

Neither is there any agreement as to the effect on the testis following the ligation of its blood vessels. Miflet [181] in 1879 held as a result of ligation of the internal spermatic artery in the dog that this vessel is an end artery and that its ligation causes atrophy of the testis. Examination of his protocols shows, however, that the degeneration in the germinal epithelium is only at the periphery of the tubules. Since then numerous anatomic researches on the blood supply * of the testis have been made in both man and dog. Janisch,[135] Colle,[48] Worms [297] and Picque and Worms [210] all state that the testis derives its arterial blood supply from three sources. The main source is through the internal spermatic artery which establishes anastomoses with the artery to the vas deferens and the external spermatic artery from the deep epigastric. No anastomotic flow occurs between the scrotal vessels and the arteries in the spermatic cord. After section of all the vessels to the testis, however, Colle [48] states that an anastomosis may obtain between the peripheral ends of the funiculoepididymospermatic system and the scrotal vessels sufficient to prevent gangrene of the testis when the usual source is interrupted. Pellanda and Neuhaus [199] fail to mention the external

* Enderlin [80] states that the testis will tolerate total occlusion of the blood supply for sixteen hours.

spermatic artery in their studies of the arterial circulation of the testis. Pellanda * also minimizes the importance of the deferential artery. Ludwig and Tomsa [172] state that the blood supply of the testis in the dog is the same as in man. Griffiths [113] finds that the vascular arrangement in man and dog are much the same. Schmidt [235] has studied the circulation of the testis in both man and dog and states that the comparison is not so complete as Ludwig and Tomsa [172] indicate. The source of supply is the same but the disposition of the vessels slightly different. The internal spermatic artery is more twisted in the dog and doesn't divide into two branches as soon as in the human being. Ellenberger and Baum [79] state that an anastomosis obtains in the dog between the three

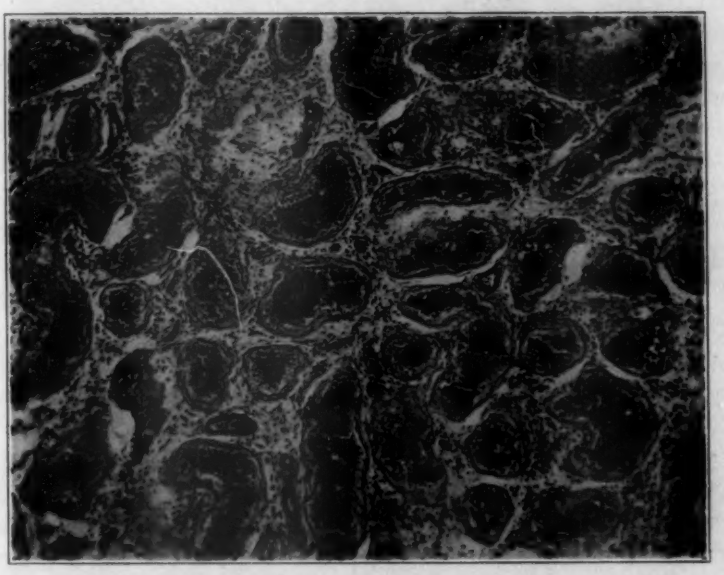

Fig. 20.—Testis of a man of 24 ill four years with pulmonary tuberculosis; no mature germinal cells are present; spermatogonia, however, are numerous.

vessels mentioned above. Experiments on the dog's testis are therefore applicable in the case of man.

In 1902 Mignon [182] in France advocated the section of all the vessels in the spermatic cord, with the exception of those accompanying the vas deferens, as a measure to aid low fixation of the testis in the scrotum in orchidopexy for incomplete descent. The following year, Bevan [17] independently in this country concluded from operations on varicocele in which he had sacrificed all the vessels in the spermatic cord except those accompanying the vas and in which no apparent interference with nutrition had occurred, that these vessels "could be safely sacrificed in

* Pellanda: Internat. Monatschr. f. Anat. u. Phys. **20**:240-265, 1903.

those cases where it is necessary to divide them in order to bring the testicle well down into the scrotum." Since then, this procedure has frequently been practiced with varying results.[136, 152, 184, 206, 290]

Previously Griffiths had demonstrated on dogs that ligation of all the vessels except those accompanying the vas deferens always results in atrophy. Griffiths [113] performed this experiment five times and only in one instance was the testis normal. But in that case the "ligature could not be found and free communication had become established as injections passed readily along the spermatic artery into the testis." In all the other instances cyanotic destruction, sloughing testis or extensive degeneration were noted. Griffith [113] did one experiment ligating the internal spermatic artery and the deferential artery; necrosis of the testis followed. In ligations of the internal spermatic artery alone, destructive changes were noted in the testes examined a few days after the ligation. But when a longer period of time intervened, the testis was found to be normal. Griffiths reasoned that the establishment of the normal histology was due to collateral circulation.

Alessandri [4] found that ligation of the spermatic artery and veins in the pampiniform plexus always caused degenerative changes. Ligation of the artery alone occasioned nutritive disturbances but no atrophy. Ligation of the artery to the vas deferens was without effect. Martini observed only a transitory effect on the testis after ligation of the internal spermatic artery.

Gangrene of the testis did not occur in experiments done by Moschowitz [196] in which the main bundle of vessels was ligated in dogs. Gessner [105] observed atrophy of the germinal epithelium of the testes in five dogs in which the same procedure was carried out. More recently Koyano [147] has practiced ligation in dogs of the vessels extraperitoneally internal to the anterior superior spine in order to eliminate the factor of trauma. In his hands, ligation of the internal spermatic vein provoke the least change in the germinal epithelium. Ligation of the internal spermatic artery and vein was followed by slight but more definite degenerative phenomena in the germinal epithelium. The greatest amount of atrophy Koyano [147] observed after ligation of the internal spermatic artery alone. He therefore believes that the procedure of vessel section in the treatment of undescended testis is rational and justifiable.

Haberer [117] has worked out in detail the venous outflow of the testis and epididymis. A great venous communication exists about the testis and epididymis Haberer states, and he finds that the blood may leave by four possible routes. Most of the return occurs through the internal spermatic vein, a lesser amount through the external spermatic vein, and portions through the vein of the epididymis and the vein of the vas deferens. The external spermatic vein empties into the deep epigastric;

the veins of the vas deferens into the plexus about the seminal vesicles, and the vein of the epididymis into the internal spermatic. Anastomoses between the veins, it is apparent, therefore, occur only in the lower portion. Interruption of the veins in the pampiniform plexus below the anastomoses will interfere considerably more with the circulation in the testis than the ligation of the internal spermatic vein alone high in the extraperitoneal region. This fact has long been known in the treatment of varicocele,[12, 131, 132, 146, 213] and the high ligation of the vessels has superseded the scrotal resection of veins. Koyano's observation, therefore, that ligation of the internal spermatic artery and vein in the

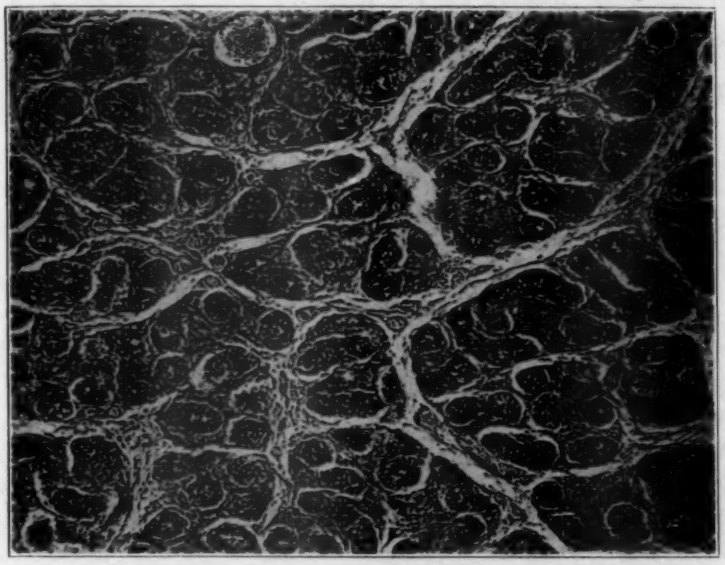

Fig. 21.—Testis of a seven months premature infant (one of triplets; the histologic picture was the same in all testes; the testes in each instance were still within the abdomen); the lumen has not been established in the tubules; Sertoli cells and spermatogonia alone constitute the walls of the seminiferous tubules; red blood cells are present in the intertubular spaces.

extraperitoneal region is without considerable effect on the histology of the testis is interesting, but amounts to virtually the same thing as my ligation of the internal spermatic artery and anterior group of veins in the pampiniform plexus; this ligation, as I have shown, may be compatible with a fairly normal spermatogenesis in the tubules. Marked diminution in size of the testis, however, occurs.

In the operation as practiced for scrotal fixation of the undescended testis, when vessel section is done, all the vessels except those in immediate relation with the vas are severed. Only rarely are the vas and the vessels that accompany it of insufficient length. The reaction of the

testis to division of the internal spermatic artery and vein in the retroperitoneal space do not therefore obtain in the operation as done for undescended testes.

Ligation of the internal spermatic artery and pampiniform plexus always results in atrophy of the germinal epithelium and interstitium of the testis as well. Statements [122] to the effect that ligation of these vessels is without deleterious effect on the testis will not bear investigation. A comparison of the photomicrograph that represents the testis recovered from a patient on whom orchidopexy with vessel section had been done a few years previously with what obtains in the dog is quite convincing as to what happens to the testis when all the vessels except those accompanying the vas deferens are divided.

Transference of the testis from the scrotum in adult dogs always results in atrophy. Whether the testis is placed in the retroperitoneal region, the peritoneal cavity or the inguinal region, degeneration of the germinal epithelium always occurs. Ligation of the vas does not cause atrophy. Ligation of the internal spermatic artery and with it the nerve supply to the testis does not cause a disseminated destruction of the seminiferous tubules.

When the testes are replaced in the scrotum, a fairly normal condition is reestablished. Spermatozoa are found in the tubules and in the epididymis. Moore [191] has recently also shown that regeneration of the germinal epithelium occurs in the seminiferous tubules of guinea-pigs and rabbits after scrotal replacement following elevation to the peritoneal cavity.

The scrotum, therefore, is essential to the normal development of a testis, and Moore [192] has rightly ascribed to the scrotum an important physiologic function.

Just what the scrotum affords the testis that is lacking elsewhere has been an interesting but mystifying problem. Piana concluded from his experiments that the temperature in the abdomen was unfavorable.[260] More recently Turner [275] examined the testes of perch during different seasons and found that with fall in temperature of the water spermatogenesis began and ceased with increase in temperature. Later Crew [61] pointed out that the scrotum was well equipped for local heat regulation in that no insulating layer of fat intervened between the skin and the dartos muscle; he suggested that this circumstances accounted for the aspermatic condition of cryptorchid testes. Benedict and Slack [11] had previously demonstrated that a constant body temperature is only reached at a depth of from 6 to 8 cm. and that a temperature gradient of 5 degrees obtains between the body cavities and the external surface. Fukui [102, 104] in Japan has recently observed that exposure of the dog's scrotum to the sun at temperatures of 44-49 C. for two hours produced degenerative changes in the germinal epithelium. The same occurred if the dog's

scrotum were immersed in water at the same temperature. The lowest temperature that will cause these changes he found to be 40 C. The higher temperatures required much less time to bring about the same effect. Moore and Quick [193] have observed these degenerative changes in the testis of guinea-pigs when exposed to increased temperature. Moore and Oslund [194] have also shown that following insulation of the scrotum of a ram with successive layers of woolen batting and cloth the same aspermatic condition is produced. Moore and Quick [193] observed a difference of 8 degrees C. between the temperature of the scrotum and abdominal cavity in guinea-pigs.

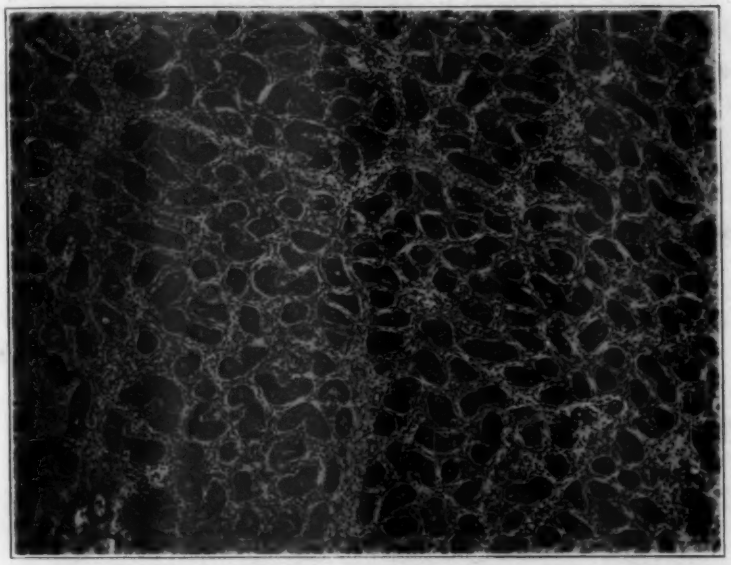

Fig. 22.—Testis of a 2 year old child.

These data would indicate that the scrotum exerts a beneficial influence on the testis through its ability to maintain a constant temperature. Whether the thermal explanation is correct or not, at least the scrotum is very necessary to the maintenance of a normal histologic picture in an otherwise normal healthy gland.

There are a few other facts that would support the heat factor as being of considerable significance. Hart [123] observed that elevation of the body temperature in gray mice when kept in iron cages at a temperature of 40 for five days causes atrophy of the germinal cells. It has long been known that in acute febrile diseases a degeneration of the germinal epithelium occurs. Stigler [259] showed that a temperature of 40.2 for four hours would cause the sperm to lose their motility.

The germinal epithelium apparently is sensitive to injury and a number of other agents can bring about its disappearance. Acute febrile

disturbances,[195] chronic debilitating diseases,[121, 145, 277] chronic alcoholism,[288] starvation [55, 170, 248] and vitamin free diets [5, 299] have all been known to bring about the same condition. Adler [2] reports injury to the seminiferous tubules after iodine administration. In one case coming under my observation this change was not noted.

In 1903 Albers-Schönberg [3] called attention to the sterility that occurs after exposure to the roentgen rays. Numerous observations [34, 35, 125, 148, 246] since then have corroborated this finding. As in the cases of starvation, acute and chronic febrile diseases, the removal of the cause enables the seminiferous tubules to be rehabilitated. So here the effect is usually transitory, unless the spermatogonia have been destroyed. In the prepuberty testis in which spermatogenesis has not been established

TABLE 1.—*Average Weight of Testis from Birth to Eighteen Years (Mita)*

| | Gm. | | Gm. | | Gm. |
|---|---|---|---|---|---|
| New-born ..... | 0.5 | 1 year ..... | 0.7 | 2 years..... | 1 |
| 5 years..... | 1.16-1.23 | 11 years..... | 1.93 | 12 years..... | 1.9 |
| 13 years..... | 4.50 | 15 years..... | 11 | 17 years..... | 16 |
| 18 years..... | 17 | | | | |

TABLE 2.—*Average Weight of Testis from Birth to Fifteen Years (Wwedensky)*

| | Testis Weight in Grams | | Epididymis Weight in Grams | |
|---|---|---|---|---|
| | Right | Left | Right | Left |
| New-born ..... | 0.2 | 0.196 | 0.12 | 0.12 |
| 3 months..... | 0.52 | 0.51 | 0.19 | 0.19 |
| 1 year..... | 0.72 | 0.71 | 0.2 | 0.2 |
| 1- 5 years..... | 0.86 | 0.87 | 0.19 | 0.2 |
| 8-10 years..... | 0.8 | 0.82 | 0.24 | 0.24 |
| 11 years..... | 1.2 | 1.3 | 0.4 | 0.39 |
| 12 years..... | 1.5 | 1.5 | 0.42 | 0.42 |
| 14 years..... | 1.48 | 1.5 | 0.52 | 0.52 |
| 15 years..... | 6.79 | 6.83 | 1.00 | 1.00 |

this reaction is minimal.[294] No degenerative phenomena are in evidence, but edema and red blood cells may be present.*

Wwedensky [298] in an examination of forty-six cases from birth to fifteen years found the results given in table 2.

Elsewhere only brief mention has been made of the anatomy of the prepuberty testis. The general conformation of the testis as in the adult is ovoid, but bean shaped organs with a concave posterior aspect and a prominent hilum are not infrequent. Büdinger [39] has stressed this finding as significant in incompletely descended testes, but Gundobin [116] says this is not unusual in the normal. Mita [183] has weighed and microscopically examined 113 testes in ages from birth to 18 years. All but twenty-two of these were in children under 13. He appends a table of average weights (table 1), the amount being designated in grams or fraction thereof for one testis.

* Schultze [241] and Simmonds [244] state that this is a frequent finding in the apparently normal new-born.

Reich * has recently reported 426 testes measurements in the living by the use of calipers in 221 boys of various ages from birth to 16 years of age. A study of his measurements shows that the testis scarcely shows any definite appreciable growth before the eleventh year. Table 3 is a record of his measurements.

From these weights it is apparent that the testis increases but slowly in weight from birth to puberty. Scammon [232] states that the weight of the two testes at birth with their epididymides is about 2 Gm. During the first two years of life this weight is doubled, but until the thirteenth or fourteenth year the increase is very gradual, the average combined

TABLE 3.—*Measurements of Testis from Birth to Sixteen Years in 221 Boys (Reich)*

| Age | No. of Cases | Left | | Right | |
|---|---|---|---|---|---|
| | | Length, Cm. | Breadth, Cm. | Length, Cm. | Breadth, Cm. |
| 0- 1 month | 6 | 1.5 | 0.7 | 1.6 | 0.8 |
| 1- 2 months | 7 | 1.6 | 0.8 | 1.6 | 0.8 |
| 2- 3 months | 11 | 1.6 | 0.8 | 1.6 | 0.8 |
| 3- 4 months | 7 | 1.6 | 0.8 | 1.6 | 0.8 |
| 4- 5 months | 4 | 1.7 | 0.8 | 1.7 | 0.8 |
| 5- 6 months | 6 | 1.7 | 0.8 | 1.7 | 0.8 |
| 6- 7 months | 4 | 1.6 | 0.8 | 1.6 | 0.8 |
| 7- 8 months | 5 | 1.6 | 0.8 | 1.6 | 0.8 |
| 8- 9 months | 5 | 1.6 | 0.8 | 1.6 | 0.8 |
| 9-10 months | 4 | 1.6 | 0.8 | 1.6 | 0.8 |
| 10-11 months | 5 | 1.6 | 0.8 | 1.6 | 0.8 |
| 11-12 months | 7 | 1.6 | 0.9 | 1.6 | 0.9 |
| 1- 2 years | 28 | 1.7 | 0.8 | 1.7 | 0.9 |
| 2- 3 years | 13 | 1.6 | 0.9 | 1.6 | 0.8 |
| 3- 4 years | 10 | 1.6 | 0.8 | 1.6 | 0.8 |
| 4- 5 years | 5 | 1.6 | 0.8 | 1.6 | 0.8 |
| 5- 6 years | 6 | 1.7 | 0.9 | 1.7 | 0.8 |
| 6- 7 years | 14 | 1.7 | 0.9 | 1.7 | 0.9 |
| 7- 8 years | 11 | 1.7 | 0.8 | 1.7 | 0.8 |
| 8- 9 years | 13 | 1.5 | 0.9 | 1.6 | 0.8 |
| 9-10 years | 8 | 1.7 | 0.9 | 1.7 | 0.9 |
| 10-11 years | 11 | 1.7 | 0.9 | 1.7 | 0.9 |
| 11-12 years | 8 | 1.9 | 0.9 | 2.0 | 1.0 |
| 12-13 years | 7 | 2.3 | 1.2 | 2.3 | 1.2 |
| 13-14 years | 6 | 2.8 | 1.4 | 2.8 | 1.4 |
| 14-15 years | 6 | 2.8 | 1.4 | 2.9 | 1.5 |
| 15-16 years | 4 | 3.5 | 2.0 | 3.6 | 2.0 |

weight of the testes and epididymides then being about 4 Gm. Mita's [183] figures show that the sudden increase in weight occurs about the thirteenth year. In Wwedensky's [298] statistics this marked increase is delayed until the fifteenth year. At all events, the increase in weight from the end of the first year to the time at which a sudden increase occurs is but a gram for each testis. Reich's data show that there is practically no increase in size of the testis until the beginning of the twelfth year, and Reich states that there is no growth of the testis during the first eleven years of life.

Spangaro [253] studied the histologic changes in testes from birth to old age and noted the similarity between those of the new-born and the prepuberty testes. Only with the increase of weight incident to puberty

* Reich: Testikelmessungen bei Kindern, Jahr. f. Kinderh. **105**:290-300, 1924.

and the occurrence of spermatogenesis does a marked change in the histology occur. In the testis of the new-born there is no real lumen in the tubules. Two or three irregular rows of cells almost completely fill the tubule. The spermatogonia may be present singly or in groups. Spangaro [253] states that the proportion of spermatogonia to Sertoli cells is from 1:35 to 1:200 to 1:400. In the preadolescent period the only changes that occur are the establishment of a central lumen; a definite arrangement of the Sertoli cells, and an increase in the number of spermatogonia, such that the proportion of spermatogonia to Sertoli cells increases to 1 spermatogone to every 12-20 Sertoli cells. However, Spangaro [253] states that a definite relationship between the number of

Fig. 23.—Testis of a 5 year old child; there is more definite outline of tubules than in figure 22 and beginning lumen formation.

spermatogonia in the tubules and the age of the child does not exist. The morphology of the spermatogonia themselves throughout the period from the first to the fourteenth year Spangaro finds is much the same as that of the new-born.

Mita [183] concurs in all of Spangaro's findings, but states that a rapid rate of growth occurs between the twelfth and the thirteenth years. Spermatogenesis was first observed at 13.

Wwedenski [298] classifies the changes that occur in the testis of the young in the following manner.

During the first fetal period from the fourth to the eighth month the tunica albuginea consists of but one layer and is of fine connective

tissue. Spermatogonia and Sertoli cells are present in the tubules. The average diameter of the tubules is 60 microns. The interstititial cells appear prominent and the connective tissue between the tubules is quite delicate.

In the second period from birth to 14 years, the tunica albuginea takes on a fibrous character and consists of two layers. The connective tissue between the tubules contains elastic fibers that do not become prominent, however, until 6 years of age. The epithelium of the tubules consists of nonfunctioning spermatogonia and the Sertoli cells.

During the third period beginning with the fifteenth year the tunica albuginea and corpus Highmori become thicker. The diameter of the

Fig. 24.—Testis of an 11 year old child; no mature germinal cells; increase in number of spermatogonia as compared with Sertoli cells.

tubules increases from 60 to 85-90 microns, and the adult germinal cells become differentiated.

It has previously been pointed out that the spermatogonia are the most resistant to injury and persist in the seminiferous tubules after transplantation of the testis from the scrotum for some time after all the other germinal cells have disappeared. In the prepuberty dog's testis in which only Sertoli cells and spermatogonia exist in the tubules, no change is observed in the histology of the organ when the gland is placed in the abdominal cavity or inguinal region under the same conditions that cause disappearance of the germinal epithelium in testes of the adult dog.

It is true that the spermatogonia in the mature dog's testis after a prolonged transference from the scrotum do disappear, and when replaced in the scrotum the mature germinal cells cannot be regenerated. When spermatogenesis supervenes the resistance shown by the resting spermatogone of the young animal is greatly diminished and it becomes as the other germinal cells, though in less degree, the victim of its new environment.

The ability of the testis to regenerate its structure has been the subject of a number of researches.[110, 133, 231] Anatomists are divided concerning the mode of origin of the germinal cells. One school believes that the Sertoli cells are the progenitors of the entire germinal epithelium,[214] the other that the Sertoli cells have only a nourishing function [10] and that the mature sexual cells are all developed from the spermatogonia that are present at birth. If the dog's testis is allowed to remain in the peritoneal cavity until all the spermatogonia have disappeared, no regeneration of the germinal epithelium is observed when the testis is replaced in the scrotum.

Before puberty the experimentally undescended testis develops much like its fellow in the scrotum. But if allowed to continue in its new habitat, it will make an attempt to maintain a normal spermatogenesis, but degenerative changes frustrate its attempts.

In how far can these data be construed to have any bearing on the human testis? It has been shown that no destructive changes are observed in the testes of young dogs when transferred to new surroundings outside the scrotum. It has been offered in explanation that the germinal cells in the testis at this time are few, the testis itself is small and only the onset of spermatogenesis makes the testis sensitive to injury. Transference of the testis in the adult dog from the scrotum always results in atrophy, but replacement in the scrotum at not too late a date restores the spermatogenic function again.

Frequent reference has been made throughout this article to Moore's excellent work on experimental cryptorchidism. Recently [191] he has shown that the testis of the rat and guinea-pig when placed in the peritoneal cavity will regenerate its germinal epithelium if redeposited in the scrotum. He concludes that this unquestionably demonstrates that the undescended testis is degenerate because of its position. The first experiments in this study were on guinea-pigs and rabbits. It occurred to me early, however, that in order to draw any conclusions relevant to the undescended testis in man an animal must be used in which the testis is always resident in the scrotum. The testes of guinea-pigs and rabbits, like those of all rodents, can be drawn up at will into the abdomen.[205] Tandler and Grosz [264] studied the seasonal changes in the testes of the mole. They found that during rest in the month of March the germinal epithelium reaches its highest development and then gradually wanes.

Rasmussen [215] and Hansemann [121] noted that the germinal epithelium disappears in the hibernating woodchuck. Marshall [176] says that in rodents the testes go back into the abdomen after rest, and that in testes of tame rabbits in winter there is little evidence of spermatogenesis. These reports have been confirmed by others.[59, 114, 166]

After finding in the abdominal transplantation of the testes in rabbits that the control left in the scrotum had also slipped into the abdomen, I abandoned rodents as the subject of experiment and chose the dog whose testis like that of man is continually resident in the scrotum. I am aware that Regaud [218] examined the testes of rats and found spermatogenesis present at all seasons of the year, but the scrotum is not the normal location of rodents' testes and I feel that it would be hazardous to apply to a testis whose habitat is always the scrotum the same standard that obtains in a testis that can be drawn into the abdomen at will. In the human being "ectopie en retour" always results in atrophy. In rodents this is physiologic.

A group of animals known as Testiconda,[205, 270] including the elephant, walrus, seal and camel, normally have a testis in the abdomen or inguinal region. In these animals this position of the testis is compatible with fertility. In the ram, boar,[9] the bull, horse [126, 127] or dog this position of the testis as in man is associated with an atrophic condition of the testis. Hobday [126] states that the nearer the testis approaches the scrotum in horses, the more likely is that testis to exhibit spermatozoa.

Numerous authors state that the anatomy of the human undescended testis is normal before puberty.[20, 161, 174, 252] Unfortunately only few of these have been obtained for microscopic examination. However, the examination of a small number of these have been recorded and in practically every instance they have been described as normal. Felizet and Branca,[86, 87, 88, 89, 93] to whom we are indebted for a number of these examinations, though believing that a primary atrophy of infancy and a secondary postpuberty deterioration bring about the degenerate condition of the undescended testis, nevertheless state that the phenomena of degeneration are much less frequent in the undescended testis of the young subject than in the adult. Their examinations of undescended testes in young subjects show that a germinal epithelium represented by spermatogonia, spermatocytes and spermatids is elaborated.[86, 89] They believe that atrophy occurs before spermatozoa are formed. A testis that can produce spermatocytes can also produce spermatozoa and maintain a normal spermatogenesis under the proper environment as observed in scrotal replacement of abdominal testes in dogs.

Felizet and Branca [86, 89] in two articles on the histology of the undescended testis in the young record the examination of twenty-four undescended testes in their first paper, fourteen of which were in the

prepuberty or puberty testes. In their following article they report twenty-six cases; eleven of which were in the young. Excerpts from the descriptions of the testes in their second publication on the subject are tabulated. Their conclusions and findings were the same in both articles.

Of the fourteen undescended testes examined in the first series, eight were said to be normal for the age. (Included among these, eight were testes of subjects from 11 to 14 years.) One in a boy of four was tuberculous. Of the remaining five, all occurred in subjects 13 years of age and the description given these was that the germinal epithelium was not commensurate with what one should expect at this age. From the researches of Spangaro,[253] Wwedenski[298] and Mita,[183] however, it is apparent that the histology of the new-born child's testis and that of the boy of 13 before spermatogenesis occurs are very similar.

Tabulation of descriptions of the young testes in Felizet and Branca's second series follows:

1. Observation 29. Age, 6. Spermatogonia in repose; some of these in mitosis.
2. Observation 33. Age, 9. The seminal tubules were constituted by epithelial cells and a number of male ovules (spermatogonia). "The canals are full but rare." The diameter of the canals varied from 26 to 45 microns. Only a maximum of thirteen seminal canals could be counted in any one fixed field with a number 4 objective. (In a footnote at the bottom of the same page they state that as many as from twenty-five to thirty tubules have been counted in another undescended testis in a boy of 9.)
3. Observation 34. Age, 15. Numerous spermatogonia in mitoses; degenerative changes also apparent.
4. Observation 36. Age, 14.5. Numerous spermatogonia, some in repose, others in mitosis; also spermatocytes.
5. Observation 39. Age, 17. Spermatogonia and spermatocytes; also degenerative changes.
6. Observation 40. Age, 8. Tuberculous testis.
7. Observation 42. Age, 6. Spermatogonia present, as many as five per tubule; lumen present in most of the tubules; in places desquamated elements from "male ovules" and Sertoli cells. (The latter statement is certainly open to doubt.)
8. Observation 44. Age, 12.5. Numerous spermatogonia in repose; many in process of division; also spermatocytes of first order; a number of Sertoli cells were in the process of degenerating and contained fat.
9. Observation 45. Age, 12. Some of cells were filled with fat; some were desquamating into the central lumen; did not stain as well as normally.
10. Observation 46. Age, 14. Chromatolysis of some spermatogonia; others in the process of proliferation; a few spermatocytes were present in several stages of mitosis.
11. Observation 47. Age, 14. A few areas of degeneration; some infantile tubules present; some showed vacuolated spaces from which the germinal cells were disappearing; some tubules were of normal diameter and showed spermatogonia and spermatocytes in mitosis.
12. Observation 50. Age, 14. Spermatogonia and numerous spermatocytes; also evidences of degeneration.

Bezancon mentions the examination of two undescended testes in the young. One of these was an inguinal testis removed from a boy of 13. When compared with a scrotal testis of a boy of the same age removed at postmortem, Bezancon states that there was no difference and that the histology of the undescended testis was normal. He cites one other case, that of a boy of 1 year whose undescended testis was smaller than the scrotal testis, but here there was also an abnormal blood supply in that the spermatic artery arose from the aorta just above its bifurcation.

Staemmler reports the examination of three prepuberty undescended testes:

1. Left inguinal testis, age, 15; weight of descended organ, 7 Gm.; weight of undescended organ, 3 Gm.; degenerative phenomena present in the undescended testis.
2. Right inguinal testis, age 6; same weight and appearance as the descended testis.
3. Bilateral inguinal testes, 4¼ years; "Kyrle's undeveloped testes."

A word of explanation here is necessary as to what the so-called underdeveloped testis of Kyrle [154, 155, 156, 157] is. Kyrle examined 110 testes in children. Eighty-six of these he found to be grossly hypoplastic and of the twenty-four, one-half were microscopically hypoplastic. Diamantopoulos [67] concurs in Kyrle's observation and finds that a normal testis in the young is a rare occurrence. Spangaro,[253] Mita [183] and Wwedenski's [298] descriptions of the normal condition in the prepuberty testis would agree with what Kyrle and Diamantopoulos describe as a hypoplastic gland. Reich states that a testis is only to be described as infantile if it fails to assume the normal growth after the eleventh year. Schultze's [241] findings are in agreement with those of Spangaro, Mita and Wwedenski. Voss,[284] using Kyrle's criteria, was able to find only seven normal testes in 117 examinations of children under 11. In thirteen boys from 12 to 20, however, the normal condition was observed in twelve, or 93.8 per cent. Voss makes the interesting comment that a hypoplastic child's testis can apparently assume the normal condition at puberty. The primary atrophy of undescended testes that Felizet and Branca [86, 89] recognize in infancy is apparently the so-called Kyrle's underdeveloped or hypoplastic testis, a normal finding in prepuberty testes.

The surgeon who palpates the undescended testis of the child and pronounces it atrophic commits the same error, not taking cognizance of the fact that the scrotal testis until spermatogenesis supervenes is also to palpation an "atrophic" organ.

There are a few cases on record in which sperm production or children have followed marriage after bilateral orchidopexy in the father. In

all these instances, however, the operation was done after puberty * and no record was obtained as to the absence or presence of spermatozoa before the operation. Because of the age at which the operation was done, I feel that these must be regarded as instances of those cases in which a temporary spermatogenesis may occur in cryptorchids.

All these facts do, however, demonstrate that the undescended testis goes through the state in which a mature germinal epithelium is elaborated. The very fact that a certain number of cryptorchids' testes are functional in an abnormal habitat demonstrates that they are not ab ovo imperfect. The fact that degenerative changes appear, as Felizet and Branca [86, 89] have described, in the undescended testis at puberty is significant that the more mature germinal cells are produced, for the immature or prepuberty testis does not exhibit degenerative changes. Similarly, the testis of the young dog undergoes no change when elevated into the inguinal region or peritoneal cavity. The adult dog's testis is subject to degenerative changes if removed from the scrotum, but when replaced in its normal environment before all the spermatogonia have disappeared, the histology of the tubules can be restored.

Given the stimulus to development, therefore, that the scrotum affords, the undescended testis of man, if successfully placed in the scrotum before the changes incident to puberty occur, should develop normally.

## THE SURGERY OF THE UNDESCENDED TESTIS

No attempt will be made here to discuss the numerous procedures that have been suggested to deal with the undescended testis. The principles involved in the treatment of the condition will be briefly considered.

In general there are three methods practiced in the treatment of arrest of descent, viz., removal of the testis, abdominal reposition and orchidopexy. Szymankowski,[261] himself [16] the victim of malignancy in an inguinal testis, was a strong advocate of its therapeutic removal. Many support him in this belief.[267] Others urge removal of the inguinal testis only in the event of pain or other complicating factor, and still others believe that the inguinal testis should be removed [7, 173] after puberty if the other testis is in the scrotum. The testis within the abdomen has usually been left alone unless a hernia has necessitated

* Duchesne [68] reports the case of a boy with bilateral incomplete descent. At 16 an inguinal testis was placed in the scrotum; at 17 a right inguinal testis was similarly treated, but retracted to the external ring. At 18 spermatozoa were found in the semen. Froehlich [100] reports the same finding in a boy of 18 who had been operated on the year before for bilateral inguinal retention. Coley [81] observed spermatozoa in the ejaculation of a man of 30 after the bilateral operation. Coudray [83] observed a boy whose testes descended spontaneously after 11 years of age; nine years later sperm were present.

interference. In bilateral abdominal retention, operation has been urged to preserve the secondary sexual characters under the impression that cryptorchids were not infrequently like castrates. From what has gone before, it is obvious that the ideal treatment of partial descent is fixation of the testis in the scrotum without injury to the vessels.

*Age.*—The best age at which to place the testis in the scrotum also is a matter of dispute. Most writers are agreed that the operation should be done before puberty. Brocha [33] states that the operation may be performed as soon as the child is diaper broke. Mixter [185] and Eisendrath [78] believe that the operation should be done at any early age. Eisendrath, however, doesn't believe that placing the testis in the scrotum favorably affects the spermatogenetic power of such a testis. Le Joly-Senoville [161] believes that from 14 to 16 is the proper age; Duchesne,[68] from 10 to 20, and Carlier,[44] from 17 to 25. The belief that pituitary [78] or thyroid [198] extract will encourage spontaneous descent is without foundation.

A consideration of the anatomy of the prepuberty testis and the reaction of the young dog's testis to transplantation outside the scrotum, however, indicate that the operation must be done before puberty changes supervene. Wwedenski [298] believes that 15 is the age of puberty. Spangaro [253] states that independent of race and individual difference the puberty age lies usually between the thirteenth and fifteenth years. Mita [183] first observed spermatogenesis in a testis of a boy of 13. Le Prince,[164] in a study of the time at which spermatogenesis occurs, first observed the presence of spermatozoa at 13.5 years. Crampton [60] studied the physiologic age in 48,000 New York high school boys and determined from the appearance of pubescence in these children that only 6 per cent were mature at the age of 12.5-13 years. Between 14.5 and 15 years, 60 per cent were mature; at 17.5-18 years, 100 per cent had reached the mature physiologic age.

Scammon [233] believes that even in the absence of the appearance of spermatogenesis in the young testis the changes incident to puberty may begin to occur as early as the ninth year. The reposition of the testes of young pups of from 4 to 6 months of age would also support this opinion. In the elevated testes of these dogs, though the degenerative processes observed in adult dogs did not occur, occasionally large mononucleated cells with acidophilic cytoplasm made their appearance. These probably indicate that the spermatogonia are preparing for the production of the mature germinal cells. In the testes of pups of from 2 to 3 months of age, these changes are constantly absent. As soon as spermatogenesis occurs in the young dog's testis, it becomes just as sensitive to removal from the scrotum as does the testis of the mature dog.

The undescended testis, therefore, should be in the scrotum before spermatogenesis occurs. Because of the occasional occurrence of late descent, the operation may well be delayed until the ninth or tenth year; not infrequently a testis that could not be palpated will come down into the canal during the first few years of life. The presence of a hernia may urge the performance of the operation at a relatively early date. It has previously been stated that the testis increases little in size until puberty. The increase in the musculature of the vas and cremaster parallels [209] the increase in size of the testis. He who advocates waiting [44, 245] until the structures are larger would jeopardize the function of the testis. I feel that the age of choice in which to do the procedure lies between the ninth and eleventh years. Only rarely will the placing of a testis into the scrotum as late as the sixteenth year be of any functional benefit. In the patient who presents himself for operation at a late date, the result can only be cosmetic.

## OPERATIVE PROCEDURE

The modern operation of orchidopexy begins with Schüller,[240] It had been previously performed but with little success.[1, 46, 207, 226] Bevan's [16, 17, 18] admirable description of the procedure contains practically everything that is fundamental in the technic. Adherents of the procedure everywhere have since found that the separation of the testis from the vaginal process, the freeing of the vessels and vas deferens into the abdominal cavity, and the separation of the fascial coverings of the cord permit the mobilization of the testis. The suture of the lower portion of the vaginal tunic around the testis is not necessary to the success of the procedure.

In one particular, however, I cannot agree with Bevan. In many instances, as Bevan states, after the testis has been mobilized it may with ease be placed on the thigh several inches below the inguinal ligament. If the testis is then placed in the scrotum, one is surprised to find that in a few days it has retracted to the top of the scrotum. Bevan's purse string suture, it is true, will prevent the testis from being retracted out of the upper part of the scrotum, but this is not the physiologic position of the testis. Many believe that anchoring the testis at the radix peni accomplishes what nature had intended. However, such is not the case. Since Fukui's [102, 103, 104] and Moore's [191, 193] researches, it is apparent that the bottom of the scrotum is the psysiologic position of the testis. Under the influence of cold the scrotum retracts, and on warm days the scrotum is quite pendant and the normally situated testis follows the movements of the scrotum.

I therefore believe that suture of the testis to the bottom of the scrotum is necessary, but not this alone. A suture should be run through

the bottom of the scrotum and the testis maintained in its physiologic position for days under tension by mechanical fixation. *

It seems strange that the testis stripped of the cremaster and all the fascial coverings should retract. The number of poor results following orchidopexy, however, indicate that its does occur. When the mobilized gland hangs freely suspended by the vas and vessels alone, retraction signifies that one or the other has brought about the elevation of the gland.** Fecher [85] has investigated the elasticity of the vas and spermatic vessels and finds that the vessels will permit of twice as much stretching as the vas. It is physiologic for blood vessels to retract. Fecher, however, concludes that the vas is the cause of the retraction. I should infer from his experiments that the vessels being twice as elastic as the vas are much more likely to be the factor in the retraction. The greater ease with which the testis is maintained at the bottom of the scrotum after vessel section would also support this view.

In addition to lengthening of the spermatic cord by a method such as Bevan's, it has been suggested that the path the cord has to traverse can be shortened. Procedures such as those of Davison,† Wolfer [296] and Frangenheim [96] are directed toward this end. The chief increase in length that occurs, however, after division of the deep epigastric vessels or transplantation of the testis behind them is in the vas deferens and this structure is practically always long enough. The gain in length of the spermatic vessels by the maneuver is slight. Sievers [247] has suggested passing the testis through the obturator foramen.

If the internal spermatic artery and veins in the pampiniform plexus have to be divided to place the testis in the scrotum, atrophy of the germinal epithelium not only occurs but also of the interstitium. Such a testis is no longer a gland ‡ but a structure composed only of scar tissue.§ The only benefit to the patient in such a procedure over removal of the testis is the comforting feeling that there is something in the scrotal pouch.

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* For a discussion of methods of fixation after orchidopexy, reference should be made to Sievers [247] and Bruskin.[37] Attempts at establishing an artificial synorchidism [179, 274] or fixation of the testis outside the scrotum are procedures that have nothing to recommend them.

** For a discussion of results following orchidopexy, reference should be made to Bevan,[39] Dardel,[65] Goeritz,[106] Burkhard,[42] Coley,[51] Mixter,[184, 182] Caulk,[45] Paschen,[208] Brocha [33] and Tuffier.[273]

† Davison: Surg. Gynec. Obst. **12**:283, 1911.

‡ The same probably obtains when the pampiniform plexus is divided in the treatment of varicocele. Ligation and section of the veins in the suprascrotal portion of the cord not infrequently includes the internal spermatic artery.[97, 181, 182] Ligation of the veins alone, especially if done high up near the internal ring, is compatible with a testis capable of spermatogenesis, but the testis usually is reduced in size.

§ The epididymis remains fairly normal.

I would advocate, therefore, as a routine procedure in complete descent or maldescent of the testis early surgical intervention. The testis wherever possible should be brought to lie at the lowest portion of the scrotum. Only in a scrotal testis will the germinal epithelium develop normally. A high scrotal testis is better than one in the inguinal region or one retained within the abdomen. Abdominal reposition of the testis is preferable to vessel section. In such an event, the testis is probably better placed in the retroperitoneal space. If placed in the peritoneal cavity,* torsion is more likely to occur.[286] A tender or painful testis in the inguinal area that can not be gotten into the scrotum without vessel section may as well be removed, for if replaced within the abdomen not infrequently it continues to be painful.[238] An abdominal testis still maintains its internal secretion; a testis with the vessels cut is functionless. Castration in the uncomplicated undescended testis is rarely indicated. One-sixteenth of a normal testis [167] suffices to permit the secondary sex characters to develop normally in the rabbit and guinea-pig, and man probably would do very well with one. Hypertrophy of the remaining organ, however, does not occur [166] after castration. Malignancy of the testis is rare, more common in the undescended than in the scrotal testis. Scrotal fixation does not diminish the possibility of malignancy. Why remove such an organ prophylactically when it is so seldom the seat of malignancy, when we fail to apply the same rule to structures in which malignancy is not unusual?

## SUMMARY

The testes of adult dogs have been placed in the inguinal region and the peritoneal cavity. Loss of the germinal epithelium always follows. These changes are not observed in the prepuberty dog's testis when placed under similar experimental conditions. Ligation of the vas deferens does not result in atrophy of the germinal cells nor in hypertrophy of the interstitium. Section of the internal spermatic artery is followed always by diminution in size of the dog's testis and by scattered degenerative changes in the tubules; spermatogenesis still continues. Ligation of the internal spermatic artery with either the anterior or posterior group of veins in the pampiniform plexus is followed by the same change that accompanies ligation of the artery alone. Ligation of the internal spermatic artery and all the veins in the pampiniform plexus always results in total destruction of the testis. The preservation of the tunica vaginalis testis is not necessary for the development of a normal gland. Replacement of the dog's testis in the scrotum after it has been resident in the peritoneal cavity or inguinal region until most of the germinal epithelium has disappeared (only spermatogonia per-

* If the testis is placed in the peritoneal cavity, the vas deferens should be divided, for should gonorrheal epididymitis occur, peritonitis would follow.

sisting) will be followed by regeneration of the mature germinal cells and normal spermatogenesis. In the adult dog only a scrotal testis is normal. The testis is very sensitive to injury and in all procedures a sufficient length of time must be allowed to intervene to preclude damage due to the manipulation alone.

Undescended testes in the human adult are practically always aspermatic. These testes, however, do elaborate the mature germinal cells, but the aberrant position of the testis does not permit of the continuance of spermatogenesis. The prepuberty testis and the testis of the new-born differ but slightly in weight and the histology is practically the same. The undescended prepuberty testis is histologically similar to the scrotal testis of the same age. If placed in the scrotum without vessel damage before puberty, the undescended testis will develop normally. Ligation of all the vessels to the testis with the exception of the artery and vein accompanying the vas deferens is followed by destruction of the testis. Scrotal fixation does not minimize the possibility of an undescended testis becoming malignant. Castration in the absence of complication is too radical a therapy in the management of undescended testes.

## CONCLUSIONS

1. The undescended testis owes its imperfection to its position.
2. Scrotal fixation of the undescended testis in its physiologic position before the histologic changes incident to puberty occur will enable it to develop normally.

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# CARDIAC OUTPUT IN THE DOG DURING ETHER ANESTHESIA

## I. THE EFFECT OF ETHER ANESTHESIA ON THE CARDIAC OUTPUT *

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The condition of the heart during an anesthetic is of great concern both to the surgeon and to the anesthetist. As the primary function of the heart is mechanical, in that it serves as a pump to distribute blood to the entire body, the main interest should center in the ability of the heart to continue to supply a sufficiently large amount of blood to meet the body needs. One of the main advantages of ether over chloroform anesthesia is that the former in toxic dosages causes first a paralysis of the respiratory center, which is more easily combated than is paralysis of the heart. However, this does not signify necessarily that ether has a selective action on the respiratory center, as it is known that the heart action is poor at the time of the respiratory failure. It is possible that severe injury to the circulatory system may precede paralysis of the respiratory center.

In recent years, the studies on the effects of anesthesia have centered mainly on changes in the hydrogen ion concentration and in the alkali reserve. Menten and Crile [1] first showed an increase in the hydrogen ion concentration during ether anesthesia. Van Slyke, Austin, Cullen [2] and others have studied in great detail the changes in the blood during anesthesia. Many observations on the blood pressure changes during ether anesthesia are reported. There have been no studies directed toward determining the changes in the output of the intact heart during ether anesthesia. The statements found in the literature in regard to the effect of ether on the cardiac output are based on studies on the various functions of the circulation such as blood pressure readings, or on the effect of ether on the output of the isolated heart.

There exists a difference of opinion as to the direct effect of ether on the heart, but most of the experimental evidence supports the view that it is a cardiac depressant when administered to a sufficient degree

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for "surgical anesthesia." Cattell [3] studied the effect of ether anesthesia on the blood pressure, on the heart volume of intact cats and on the contractions of the isolated cold blooded heart. He stated:

> Observations on the heart volume of intact cats, and on the contractions of the isolated cold blooded heart, together with deductions from blood pressure records, show that the administration of ether, from its very beginning, results in a depression of the heart and a decrease in its output, which is sufficient to account for the fall in pressure in both the normal and the shocked animals.

The literature on the effects of ether on the circulatory system was reviewed thoroughly by Cattell (1923) and was summarized as follows:

> The experimental evidence briefly summarized above strongly favors the assumption that ether, in the concentrations present in ordinary anesthesia, causes a decrease in the efficiency of the heart, which might account for any fall in arterial pressure occurring under ether anesthesia.

Vernon [4] perfused the isolated turtle heart with Ringer's solution which contained ether and found that the extent of the contractions were reduced when the concentration of ether exceeded 0.10 per cent. Nicloux [5] found that the average amount of ether present in the blood in deep anesthesia varied from 0.13 to 0.15 per cent. Storm Van Leeuween [6] found that the eye reflexes were abolished when the percentage of ether in the blood by weight was 0.19. It is difficult to make deductions from the figures for ether content reported by different observers, as there is a great deal of discrepancy in the results. McWilliams,[7] experimenting on cats, found a drop in blood pressure, together with a decrease in the functional activity of the heart, when ether was administered until the corneal reflex disappeared. Cushny [8] states that ether causes the heart of the frog and of mammals to beat more slowly and weakly, and at the same time causes the heart to undergo a certain amount of dilatation.

In spite of the fact that most of the experimental evidence indicates that ether has a depressing effect on the heart, there are those who believe that ether acts as a cardiac stimulant. Gwathmey [9] states:

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8. Cushny: Pharmacology and Therapeutics or The Action of Drugs, Philadelphia and New York, Lea & Febiger, 1924.

9. Gwathmey: Anesthesia, ed. 2, rev., New York and London, the Macmillan Co., 1924.

TABLE 1.—*Effect of Ether Anesthesia on the Cardiac Output*

| Date | Weight, Kg. | Temperature, Fahrenheit | Pulse Rate per Minute | Arterial Oxygen, per Cent by Volume | Venous Oxygen, per Cent by Volume | Arteriovenous Difference, per Cent by Volume | Oxygen Capacity, per Cent by Volume | Per Cent Saturation | Oxygen Consumption, Cc. per Minute | $p_H$ | Cardiac Output, Cc. per Minute | Output per Kg. per Minute, Cc. | Output per Beat, Cc. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 5/12/26: Control; ¾ grain morphine | 8.6 | 99 | 70 | 15.36 | 8.88 | 6.48 | 17.1 | 90 | 73.95 | 7.35 | 1,141 | 132.7 | 16.3 |
| 5/12/26: After 7 minutes ether | 8.6 | 99 | 150 | 14.04 | 11.04 | 3 | 17.22 | 82 | 59.04 | 7.29 | 1,968 | 228.9 | 13.1 |
| 5/12/26: After additional ether | 8.6 | 99 | 150 | 14.40 | 11.40 | 3 | .... | .. | 58.4 | 7.30 | 1,947 | 226.4 | 13.0 |
| 5/12/26: Two hours after stopping ether | 8.6 | 98.5 | 76 | 15.24 | 8.66 | 6.58 | ... | .. | 75.64 | 7.36 | 1,148 | 133.4 | 15.1 |
| 5/15/26, 2 p. m.: Control; ¾ grain morphine | 8.2 | 101 | 120 | 13.8 | 6.97 | 6.83 | 15.5 | 94.5 | 62.52 | .... | 915 | 111.5 | 7.6 |
| 5/15/26, 3:15 p. m.: After 6 minutes ether | 8.2 | 101 | 180 | 11.51 | 8.36 | 3.15 | 17.0 | 68 | 57.2 | .... | 1,810 | 221 | 10.1 |

Protocol: 5/12/26: Control study was performed after giving ¾ grain of morphine. Dog was then given ether anesthesia through a mask for seven minutes until the eye reflexes were barely abolished, and a determination of the output was made. The ether was discontinued for a few minutes, and then the animal was again given an anesthetic for seven minutes, and another determination of the output was made. The last studies were made two hours after the ether was discontinued. The animal was quiet during all the observations.

5/15/26: Control study after giving ¾ grain of morphine. Ether anesthesia was begun at 3:15 p. m. and determinations were made six minutes later, the eye reflexes being abolished at time the specimens of blood were obtained.

TABLE 2.—*Effect of Ether Anesthesia on the Cardiac Output*

| Date | Weight, Kg. | Temperature, Fahrenheit | Pulse Rate per Minute | Arterial Oxygen, per Cent by Volume | Venous Oxygen, per Cent by Volume | Arteriovenous Difference, per Cent by Volume | Arterial Carbon Dioxide, per Cent by Volume | Venous Carbon Dioxide, per Cent by Volume | Oxygen Capacity, per Cent by Volume | Oxygen Consumption, Cc. per Minute | Cardiac Output, Cc. per Minute | Output per Kg. per Minute, Cc. | Output per Beat, Cc. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 3/15/26, 4:30 p. m.: Control study | 10.3 | 100 | 60 | 14.33 | 8.22 | 6.21 | 53.55 | 57.82 | ..... | 101.45 | 1,634 | 158.6 | 27 |
| 3/15/26, 10:00 p. m.: Control study | 10.3 | 100 | 60 | 15.66 | 9.96 | 5.72 | 44.75 | 48.95 | ..... | 94.0 | 1,644 | 159.6 | 27 |
| 3/16/26: Control study; no morphine | 10.3 | 103 | 150 | 13.74 | 7.48 | 6.26 | 41.53 | 45.15 | ..... | 99.3 | 1,594 | 154.7 | 10.6 |
| 3/29/26, 2:00 p. m.: Control study; ½ grain morphine... | 10.0 | 99 | 54 | 15.58 | 9.01 | 6.52 | 39.07 | 45.60 | ..... | 102.5 | 1,572 | 157.2 | 29 |
| 3/29/26, 4:00 p. m.: Light ether 50 minutes | 10.0 | 99 | 150 | 16.81 | 13.06 | 3.75 | 37.75 | 42.29 | 17.07 (99%) | 80 | 2,134 | 213 | 14 |
| 3/31/26: After 45 minutes deep anesthetic | 9.9 | 99 | 180 | 14.95 | 10.45 | 4.50 | ..... | ..... | ..... | 78 | 1,734 | 175 | 10 |

Protocol: Control studies on 3/15, 3/16 and 3/29/26. 3/29; determinations were made fifty minutes following the beginning of an ether anesthetic; eye reflexes were not abolished. 3/31, studies forty-five minutes following the beginning of an ether anesthetic; eye reflexes were not obtainable.

Ether acts as a direct heart stimulant during the early stages of its administration, and when, during the course of deeper narcosis, the subject is allowed to return to a lighter degree, the pulse is accelerated, and the blood pressure is slightly raised or remains constant. Ether becomes a cardiac depressant only in the later stages of anesthesia, or when a toxic amount is employed.

Muns [10] studied the effect of ether anesthesia on the blood pressure in experimental animals. He reported a rise of blood pressure in half of the animals, whereas there was a fall in the other half. Richardson stated: "Ether, like gas oxygen, drives up the blood pressure; but to a less extent, if properly given. Ether is a cardiac stimulant of more even action." Cattell [11] found that the inhalation of strong ether resulted in a sudden temporary drop in arterial pressure which returned almost to the original level by the time that the eye reflexes were abolished.

The present study was undertaken for the purpose of studying the effect of ether anesthesia on the cardiac output of the intact heart of the normal dog.

## METHODS

Dogs were used in all of the experiments. The animals varied in weight from 6 to 18 kilograms. Six of the experiments were performed on trained animals. Dogs, which had been given morphine (usually .06 Gm.) about one hour before the control determinations, were used in the remaining experiments. Marshall [12] and Blalock, Harrison and Wilson [13] have found that morphine does not alter appreciably the output of the heart. Several recent experiments have indicated that the cardiac output is diminished during the first thirty minutes after the giving of a large dose of the drug.

After the control determinations had been made, ether was administered through an open cone or through a catheter placed loosely in the tracheotomy tube. An attempt was made to obtain anesthesia of sufficient depth barely to abolish the lid reflex. This was rather difficult to do at times, due to the fact that the dog's condition changes quickly under an anesthetic. Other signs which were noted in determining the depth of the anesthetic included general relaxation, color of mucous membranes and the quality of the pulse. When the desired condition was obtained, specimens of blood were drawn with the ether cone in place, and the oxygen consumption was determined immediately after the cone was removed.

The oxygen consumption was determined by means of a Benedict spirometer with the graphic recording device. The animal was connected to the spirometer either by means of a tube placed in the trachea or by the use of an especially constructed mask which was fitted tightly over the mouth. The oxygen consumption was not determined at the same time that the ether was administered. After

10. Muns, W. E.: Am. J. Surg. (anesthesia supplement) **31**:113 (Oct.) 1917.

11. Cattell, McKeen: Studies in Experimental Traumatic Shock; Action of Ether on Circulation in Traumatic Shock, Arch. Surg. **6**:83 (Jan.) 1923.

12. Marshall, E. K.: J. Physiol. **72**:192, 1925.

13. Blalock, A.; Harrison, T. R., and Wilson, C. P.: An Experimental Study in the Effects on the Circulation and Respiration of Morphinized Dogs, Arch. Surg. **13**:81 (July) 1926.

TABLE 3.—*Effect of Ether Anesthesia on the Cardiac Output and on the Hydrogen Ion Concentration*

| Date | Weight, Kg. | Temperature, Fahrenheit | Pulse Rate per Minute | Arterial Oxygen, per Cent by Volume | Venous Oxygen, per Cent by Volume | Arteriovenous Difference, per Cent by Volume | Oxygen Capacity, per Cent by Volume | Per Cent Saturation | Oxygen Consumption, Cc. per Minute | $p_H$ | Cardiac Output, Cc. per Minute | Output per Kg. per Minute, Cc. | Output per Beat, Cc. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 5/10/26: Control study; no morphine | 14.2 | 102.2 | 100 | 15.26 | 9.84 | 5.42 | 15.43 | 99 | 118.37 | 7.45 | 2,184 | 153.8 | 21.84 |
| 5/10/26: After 35 minutes ether; no morphine | 14.2 | 101.8 | 210 | 10.50 | 7.08 | 2.82 | 17.39 | 60 | 77.5 | 7.30 | 2,741 | 192.3 | 13.05 |

Protocol: 5/10/26: Trained dog; control studies made without morphine. Studies repeated thirty-five minutes following beginning of ether anesthetic; eye reflexes were abolished.

TABLE 4.—*Effect of Ether Anesthesia on the Cardiac Output*

| Date | Weight, Kg. | Temperature, Fahrenheit | Pulse Rate per Minute | Arterial Oxygen, per Cent by Volume | Venous Oxygen, per Cent by Volume | Arteriovenous Difference, per Cent by Volume | Oxygen Capacity, per Cent by Volume | Per Cent Saturation | Oxygen Consumption, Cc. per Minute | Cardiac Output, Cc. per Minute | Output per Kg. per Minute, Cc. | Output per Beat, Cc. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2/13/26: Control study | 7.7 | 99 | 80 | 17.37 | 11.78 | 5.59 | 18.53 | 94 | 71 | 1,270 | 165 | 15.9 |
| 2/13/26: After 30 minutes ether | 7.7 | 99 | 165 | 17.19 | 13.95 | 3.24 | ..... | .. | 66.4 | 2,049 | 266 | 12.4 |

Protocol: 2/13/26, 7:30 p. m.: One grain morphine was given. 8:00 p. m.; Tracheotomy performed; 9:00 p. m.: control determinations; 11:00 p. m.: studies made thirty minutes following the beginning of an ether anesthetic. Eye reflexes were not abolished completely.

TABLE 5.—*Effect of Ether Anesthesia on the Cardiac Output*

| Date | Weight, Kg. | Temperature, Fahrenheit | Pulse Rate per Minute | Arterial Oxygen, per Cent by Volume | Venous Oxygen, per Cent by Volume | Arteriovenous Difference, per Cent by Volume | Oxygen Capacity, per Cent by Volume | Per Cent Saturation | Oxygen Consumption, Cc. per Minute | Cardiac Output, Cc. per Minute | Output per Kg. per Minute, Cc. | Output per Beat, Cc. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2/15/26, 9:15 p. m.: Control study | 7.5 | 98.6 | 72 | 14.97 | 8.42 | 6.55 | ..... | .. | 51.66 | 780 | 105 | 11 |
| 2/15/26, 10:05 p. m.: Light ether | 7.5 | .... | 108 | 15.32 | 12.79 | 2.53 | 17.92 | 86 | 51.66 | 2,042 | 272 | 18.9 |
| 2/15/26, 10:15 p. m.: Light ether | 7.5 | .... | 112 | 15.32 | 12.03 | 2.69 | ..... | .. | 54.0 | 2,008 | 268 | 18 |
| 2/16/26, 12:45 a. m.: Deep ether | 7.5 | 98.6 | 180 | 9.47 | 4.79 | 4.68 | 17.94 | 53 | 52 | 1,111 | 148 | 6.2 |
| 2/16/26, 1:00 a. m.: Deep ether | 7.5 | .... | 180 | 9.23 | 4.35 | 4.88 | ..... | .. | 53.5 | 1,096 | 146.1 | 6.1 |

Protocol: 2/15/26, 8:00 p. m., dog received 1¼ grains of morphine; 9:15 p. m., the animal was quiet, control studies were made; 10:05 p. m. and 10:15 p. m., studies after anesthesia of about thirty minutes' duration, eye reflexes present. The ether cone was removed between these two studies in order to determine the oxygen consumption. 2/16, 12:45 a. m. and 1:00 a. m., studies with the animal under deep ether anesthesia of about one hour's duration, eye reflexes were abolished. Dog died about fifteen minutes after the last observation, probably due to the ether. No hemopericardium.

the ether cone had been removed, the attachment to the spirometer was made immediately, and the oxygen consumed during the first several minutes was determined. Since the animals were rather deeply anesthetized, and since the changes in oxygen consumption were small, it is thought that little error was introduced by this method.

Specimens of blood were withdrawn while the animal was breathing ether. Arterial blood was obtained by puncture of the left ventricle or the femoral artery; venous blood, by puncture of the right ventricle. The usual precautions against contact with air were followed. The blood gas determinations were made on the Van Slyke-Neill[14] manometric apparatus. The method of Austin[15] for determining the carbon dioxide content in the presence of ether was employed. No difficulties were encountered in obtaining duplicate readings for oxygen content in specimens of blood before and after the addition of small amounts of ether, and it is thought that the values for oxygen content in this study are absolute. Nicloux[5] and, later, Ronzoni[16] have shown that the amount of ether in the arterial blood remains higher than that in the venous blood, as long as ether of the same concentration is being administered. Since the specimens of blood in the present experiments were taken while the animals were breathing ether, it is thought that any errors in the oxygen content determinations which might be ascribed to ether would tend to increase the arteriovenous oxygen content difference rather than to diminish it, as was found.

The hydrogen ion determinations were made according to the method of Hastings and Sendroy.[17] The circulatory minute volume was calculated from the

$$\frac{\text{Cc. } O_2 \text{ consumed per minute}}{\text{Amount } O_2 \text{ taken up in lungs by 1 cc. of blood}} = \text{Number of cubic centimeters of blood flowing through the lungs per minute}$$

## RESULTS

*Control Period.*—The animals were quiet while the control studies were being made. The respiratory rate and depth varied in the different animals, but were regular in the same animal in most instances. The pulse rate was slow in the animals which were given morphine. The specimens of arterial and of venous blood were normally saturated with oxygen. The cardiac output per kilogram of body weight varied little for the same animal on different dates, but there was a rather wide variation for the different animals. In general, it may be said that this figure for the large dogs is about one hundred and thirty-five cubic centimeters per kilogram of body weight, while that for the smaller dogs is about one hundred and fifty cubic centimeters per kilogram.

*Anesthetic Period.*—The animals became restless immediately and struggled when the ether was applied. The respirations became more rapid and deeper. No studies were made during the period of excitement. The amount of ether which is necessary for producing third stage

14. Van Slyke, D. D., and Neill, J. M.: J. Biol. Chem. **61**:523 (Sept.) 1924.
15. Austin, J. H.: J. Biol. Chem. **61**:345 (Sept.) 1924.
16. Ronzoni, Ethe: J. Biol. Chem. **57**:761 (Oct.) 1923.
17. Hastings and Sendroy: J. Biol. Chem. **61**:695 (Oct.) 1924.

Fick formula.

TABLE 6.—*Effect of Ether Anesthesia on the Cardiac Output*

| Date | Weight, Kg. | Temperature, Fahrenheit | Pulse Rate per Minute | Arterial Oxygen, per Cent by Volume | Venous Oxygen, per Cent by Volume | Arteriovenous Difference, per Cent by Volume | Oxygen Consumption, Cc. per Minute | Cardiac Output, Cc. per Minute | Output per Kg. per Minute, Cc. | Output per Beat, Cc. |
|---|---|---|---|---|---|---|---|---|---|---|
| 3/7/26, 5:40 p. m.: Control study | 6.8 | 97 | 60 | 16.08 | 6.60 | 9.48 | 59.04 | 623 | 91.6 | 10 |
| 3/7/26, 8:15 p. m.: After ether anesthetic for 25 minutes | 6.8 | .. | 78 | 16.02 | 10.68 | 5.34 | 66.42 | 1,244 | 183 | 16 |
| 3/7/26, 10:15 p. m.: Two hours after anesthetic was stopped | 6.8 | .. | 65 | 16.14 | 8.04 | 8.10 | 68.26 | 843 | 124 | 13 |

Protocol: 3/7/26: Healthy young dog. At 4:45 p. m., he received ½ grain of morphine; 5:15 p. m., tracheotomy was performed; 5:40 p. m., control studies were made; 8:15 p. m., determinations made after animal had received ether through the tracheotomy tube for twenty-five minutes, eye reflexes not completely abolished; 10:15 p. m., two hours after the anesthetic was stopped, studies were repeated.

TABLE 7.—*Effect of Ether Anesthesia on the Cardiac Output*

| Date | Weight, Kg. | Temperature, Fahrenheit | Pulse Rate per Minute | Arterial Oxygen, per Cent by Volume | Venous Oxygen, per Cent by Volume | Arteriovenous Difference, per Cent by Volume | Oxygen Capacity, per Cent by Volume | Per Cent Saturation | Oxygen Consumption, Cc. per Minute | Cardiac Output, Cc. per Minute | Output per Kg. per Minute, Cc. | Output per Beat, Cc. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 6/1/26, 2:00 p. m.: Control study; 1 grain morphine.... | 9.1 | 100.4 | 65 | 13.95 | 6.2 | 7.75 | 15.32 | 91 | 77.40 | 999 | 110 | 15.4 |
| 6/1/26, 4:30 p. m.: After 40 minutes anesthesia | 9.1 | 98.4 | 130 | 11.92 | 6.79 | 5.13 | ..... | .. | 70.11 | 1,367 | 150.2 | 10.5 |
| 6/1/26, 8:45 p. m.: Four hours after anesthesia and operation | 9.1 | 98 | 150 | 14.88 | 9.12 | 5.76 | ..... | .. | 79.33 | 1,377 | 151.3 | 9.2 |

Protocol: 6/1/26: At 1:30 p. m., 1 grain morphine was administered; 2:00 p. m., the dog was completely quiet, and control study was made; 4:30 p. m., completion of forty minutes ether anesthetic; eye reflexes were abolished; 4:35 p. m., abdominal incision, terminal aorta isolated but not ligated, abdomen was closed; 8:45 p. m., four hours following completion of anesthetic, dog able to walk around but unsteady. Third determinations were made.

anesthesia varies greatly in dogs just as it does in man. The time intervals separating the beginning of the anesthetic and the drawing of the specimens of blood are given in the protocols of the experiments (tables 1 to 20). This interval was varied intentionally, but in all instances sufficient time was allowed for the animal to become well relaxed. Usually the respiratory rate and depth were decreased as compared to that in the control period. The pulse rate was accelerated in all

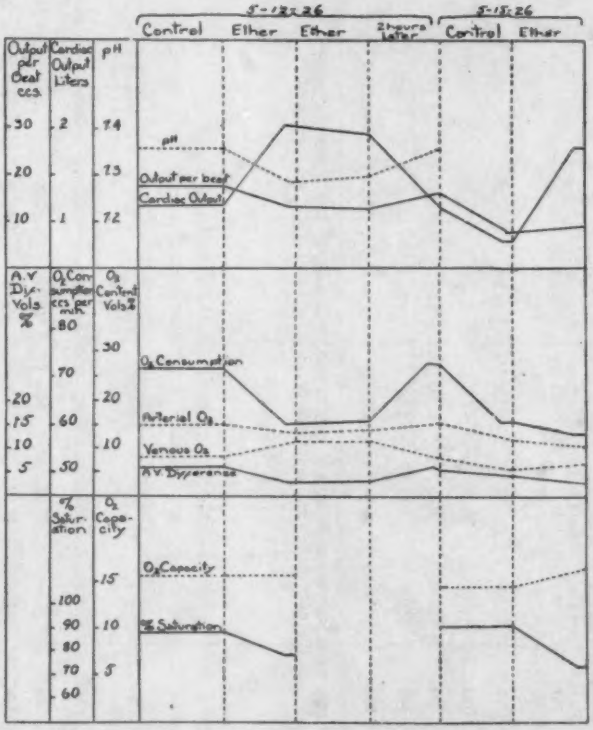


Chart 1.—This chart illustrates a typical experiment. During the anesthetic period, it is seen that the cardiac output increases, the $p_H$ falls, the arterial and venous oxygen contents approach each other, the oxygen consumption is slightly decreased, the percentage saturation of the arterial blood falls while the oxygen capacity remains about the same.

Time relations are neglected in this chart. The various functions are drawn as if constant at the time of puncture. The drawings are purely schematic.

instances, the most marked increase being found in the animals deeply anesthetized. The temperature readings showed no change during a short anesthetic, but prolonged anesthesia was accompanied by a fall of one or more degrees Fahrenheit. In an attempt to anesthetize deeply several of the animals, it was found that a toxic dose of ether was necessary to abolish completely the lid reflex. This was attempted several

TABLE 8.—*Effect of Ether Anesthesia on the Cardiac Output*

| Date | Weight, Kg. | Temperature, Fahrenheit | Pulse Rate per Minute | Arterial Oxygen, per Cent by Volume | Venous Oxygen, per Cent by Volume | Arteriovenous Difference, per Cent by Volume | Oxygen Capacity, per Cent by Volume | Per Cent Saturation | Oxygen Consumption, Cc. per Minute | Cardiac Output, Cc. per Minute | Output per Kg. per Minute, Cc. | Output per Beat, Cc. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 3/25/26: Control study; no morphine | 16 | 102.6 | 95 | 18.81 | 13.71 | 5.10 | 19.20 | 98 | 115.2 | 2,337 | 146 | 24.6 |
| Two hours later: Control study; no morphine | 16 | 102.6 | 96 | 18.70 | 13.12 | 5.58 | 19.41 | 96 | 115.0 | 2,061 | 129 | 21.4 |
| 4/8/26: Control study; no morphine | 15.5 | 102.2 | 100 | 15.74 | 9.45 | 6.29 | ..... | .. | 140.2 | 2,213 | 143 | 22.1 |
| 4/29/26: Control study; no morphine | 14.2 | 104 | 130 | 15.50 | 9.54 | 5.96 | 17.6 | 88 | 140 | 2,349 | 164 | 18 |
| 4/29/26: After 1 hour light ether anesthesia | 14.3 | 104 | 200 | 13.59 | 11.59 | 2.0 | ..... | .. | 118.1 | 5,845 | 409 | 29 |

Protocol: Control studies on trained dog without morphine on 3/25/26, 4/8, and 4/29. The animal was given an ether anesthetic for one hour following the last control study, the eye reflex not being abolished, and the cardiac output determined.

TABLE 9.—*Effect on Ether Anesthesia on the Cardiac Output*

| Date | Weight, Kg. | Temperature, Fahrenheit | Pulse Rate per Minute | Arterial Oxygen, per Cent by Volume | Venous Oxygen, per Cent by Volume | Arteriovenous Difference, per Cent by Volume | Arterial Carbon Dioxide, per Cent by Volume | Venous Carbon Dioxide, per Cent by Volume | Oxygen Capacity, per Cent by Volume | Oxygen Consumption, Cc. per Minute | Cardiac Output, Cc. per Minute | Output per Kg. per Minute, Cc. | Output per Beat, Cc. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 6/12/26, 2:30 p. m.: Control study | 14 | 103 | 84 | 15.8 | 10.96 | 4.84 | 41.59 | 43.99 | ..... | 151.29 | 3,126 | 223.3 | 37.2 |
| 5:00 p. m.: After 2 hours ether anestetic | 14 | 102.6 | 240 | 15.8 | 13.36 | 2.44 | 23.33 | 24.66 | 19.39 (82%) | 125.46 | 5,142 | 367 | 21.4 |

Protocol: 6/12/26: Trained dog, no morphine was used; at 2:30 p. m., control determinations were made; at 3:00 p. m., ether anesthetic was begun. The degree of anesthesia varied, eye reflexes were abolished several times. Specimens of blood were taken at 5:00 p. m., after two hours of anesthesia, the eye reflexes being barely obtainable.

times in one animal, and respiratory movements would stop in each instance as soon as the lid reflex was abolished.

The oxygen content of the arterial blood was slightly elevated over that in the control period in ten experiments; it remained stationary in three, fell slightly in five and was rather markedly decreased in six instances. Distinct decrease was encountered only in the animals which were deeply anesthetized. There was little change in the oxygen

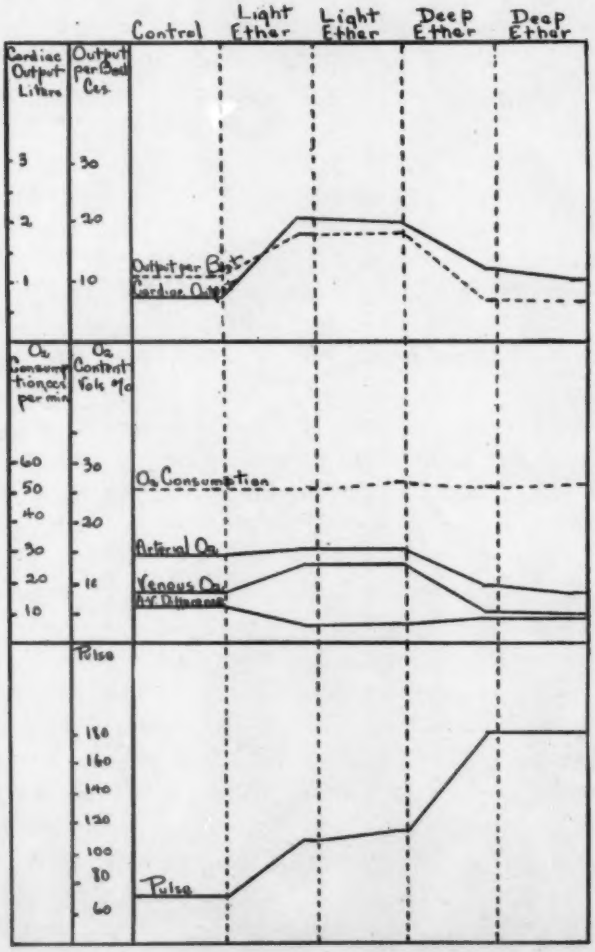


Chart 2.—This figure illustrates the decided increase in the cardiac output during light ether anesthesia, and the less marked but definite increase during deeper anesthesia. The arterial and venous oxygen contents approached each other during the anesthesia; the pulse rate rose steadily; the oxygen consumption remained about the same.

Time relations are neglected in this chart. The various functions are drawn as if constant at the time of puncture. The drawings are purely schematic.

TABLE 10.—*Effect of Ether Anesthesia on the Cardiac Output*

| Date | Weight, Kg. | Temperature, Fahrenheit | Pulse Rate per Minute | Arterial Oxygen, per Cent by Volume | Venous Oxygen, per Cent by Volume | Arteriovenous Difference, per Cent by Volume | Arterial Carbon Dioxide, per Cent by Volume | Venous Carbon Dioxide, per Cent by Volume | Oxygen Capacity, per Cent by Volume | Oxygen Consumption, Cc. per Minute | Cardiac Output, Cc. per Minute | Output per Kg. per Minute, Cc. | Output per Beat, Cc. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 6/10/26, 4:30 p. m.: Control study | 13.2 | 100.4 | 48 | 15.70 | 7.73 | 7.97 | 41.45 | 45.50 | 17.18 (91%) | 88.56 | 1,111 | 84.2 | 23.1 |
| 5:30 p. m.: After 35 minutes ether anesthesia | 13.2 | 100 | 118 | 16.41 | 12.01 | 4.40 | 38.74 | 41.85 | ..... | 84.87 | 1,929 | 146 | 16.3 |

Protocol: 6/10/26: At 3:30 p. m., 1 grain of morphine was given; at 4:30 p. m., the dog was quiet, and control determinations were made; at 4:55 p. m., ether anesthesia was begun; at 5:30 p. m., cardiac output was determined, the eye reflexes not being obtainable when specimens of blood were drawn.

TABLE 11.—*Effect of Ether Anesthesia on the Cardiac Output*

| Date | Weight, Kg. | Temperature, Fahrenheit | Pulse Rate per Minute | Arterial Oxygen, per Cent by Volume | Venous Oxygen, per Cent by Volume | Arteriovenous Difference, per Cent by Volume | Arterial Carbon Dioxide, per Cent by Volume | Venous Carbon Dioxide, per Cent by Volume | Oxygen Capacity, per Cent by Volume | Oxygen Consumption, Cc. per Minute | Cardiac Output, Cc. per Minute | Output per Kg. per Minute, Cc. | Output per Beat, Cc. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 6/8/26, 3:40 p. m.: Control study | 9.8 | 99.5 | 60 | 15.98 | 9.66 | 6.32 | 38.78 | 41.36 | ..... | 92.2 | 1,459 | 149 | 24.3 |
| 4:50 p. m.: After 30 minutes ether anesthesia | 9.8 | 97.6 | 132 | 16.58 | 13.0 | 3.58 | 39.05 | 40.82 | 17.47 (95%) | 92.2 | 2,771 | 282.8 | 21 |

Protocol: 6/8/26: Dog which had been used previously in studying the effect of a digitalis preparation on the cardiac output was used; at 2:30 p. m., 1 grain of morphine was given; at 3:40 p.m., experiment was performed; at 4:50 p. m. specimens of blood were taken after ether anesthesia for thirty minutes, eye reflexes not being abolished.

capacity of the arterial blood in the several instances in which it was determined, the tendency being toward a slight increase. In most of the experiments in which the oxygen capacity was determined, there was a decrease in the percentage saturation of the arterial blood.

The oxygen content of the venous blood usually rose about 2 per cent by volume during the anesthetic. A drop was found in several instances in which the degree of anesthesia was profound.

The oxygen coefficient of utilization (arterial oxygen content minus venous oxygen content) was decreased in all animals except three, the decrease denoting a rapid circulatory rate. Two of the three animals which did not show this decrease stopped breathing before the studies were made and were resuscitated. The change in the coefficient of utilization in two experiments is pictured graphically in figures 1 and 2.

The hydrogen ion concentration was uniformly increased, the degree not being great in any instance. Koehler [18] determined the hydrogen ion concentration of the venous blood of patients under ether anesthesia. The changes encountered by him were much greater than those reported here, but the difference is probably explained by the rebreathing method which he used as contrasted to the open cone method which was used in these experiments.

The carbon dioxide content of the blood was decreased. This fall is thought to be due to the presence of non-volatile acid metabolites and is similar to that found in diabetic and renal acidosis.

The oxygen consumption was slightly decreased in nearly every instance. The inability to obtain the oxygen consumption without removing the ether cone has been mentioned previously.

The cardiac output was increased in all experiments except three. Two of these animals were anesthetized deeply, and resuscitation was necessary. The output of the heart per beat was decreased in twenty-two instances and increased in six. The decrease was usually associated with a marked acceleration of the pulse. The changes in the cardiac output are listed in tables 1 to 20, and the percentage change is pictured graphically in figure 3.

The same results were obtained in both the trained dogs and those which were given morphine.

Several determinations of the cardiac output were made at intervals ranging from two hours to several days following the termination of the anesthetic, and in no instance was any significant decrease in the output of the heart found (tables 6 and 7).

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18. Koehler, A. E.: J. Biol. Chem. **62**:435 (Dec.) 1924.

TABLE 12.—*Showing the Effect of (1) Deep Ether Anesthesia and (2) Trauma to Intestines on the Cardiac Output*

| Date | Weight, Kg. | Temperature, Fahrenheit | Pulse Rate per Minute | Arterial Oxygen, per Cent by Volume | Venous Oxygen, per Cent by Volume | Arteriovenous Difference, per Cent by Volume | Oxygen Capacity, per Cent by Volume | Per Cent Saturation | Oxygen Consumption, Cc. per Minute | Cardiac Output, Cc. per Minute | Output per Kg. per Minute, Cc. | Output per Beat, Cc. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2/5/26, 11:30 a. m.: Control study | 10 | 99 | 70 | 18.56 | 14.51 | 4.05 | 20.25 | 92 | 70.1 | 1,730 | 173 | 24.7 |
| 2/5/26, 1:30 p. m.: Deep anesthesia | 10 | .. | 180 | 11.92 | 5.41 | 6.51 | 19.12 | 62 | 66.4 | 1,020 | 102 | 5.7 |
| 2/5/26, 5:30 p. m.: After trauma to intestines | 10 | .. | 200 | 16.93 | 10.16 | 6.74 | 19.14 | 89 | 66 | 975 (?) | 97.5 | 4.9 |

Protocol: 2/5/26: At 10:30 a. m., 1¼ grains of morphine was administered; at 11:00 a. m., tracheotomy was performed; at 11:30 a. m., the animal was quiet, and control studies were made; at 1:00 p. m., ether anesthesia was begun; the dog became deeply anesthetized (stopped breathing once), and specimens of blood were drawn at 1:30 p. m.; at 5:30 p. m., four hours following the production of a great deal of trauma to the small intestines, the cardiac output was determined. The animal died shortly afterward.

TABLE 13.—*Effect of Ether Anesthesia on the Cardiac Output*

| Date | Weight, Kg. | Temperature, Fahrenheit | Pulse Rate per Minute | Arterial Oxygen, per Cent by Volume | Venous Oxygen, per Cent by Volume | Arteriovenous Difference, per Cent by Volume | Arterial Carbon Dioxide, per Cent by Volume | Venous Carbon Dioxide, per Cent by Volume | Oxygen Consumption, Cc. per Minute | Cardiac Output, Cc. per Minute | Output per Kg. per Minute, Cc. | Output per Beat, Cc. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 6/18/26, 3:30 p. m.: Control study | 10 | 101.6 | 50 | 16.9 | 12.31 | 4.58 | 36.18 | 38.99 | 73.8 | 1,611 | 161 | 32 |
| 5:00 p. m.: After 20 minutes anesthetic | 10 | 102 | 120 | 17.64 | 15.86 | 1.78 | 35.78 | 36.04 | 84.9 | 4,770 | 477 | 40 |

Protocol: 6/18/26: At 2:15 p. m., 1 grain of morphine was administered; at 3:00 p. m., tracheotomy was performed; at 3:30 p. m., control determinations were made; at 4:40 p. m., ether anesthetic was begun; at 5:00 p. m., eye reflexes being barely obtainable, specimens of blood were drawn.

COMMENT

The changes in the hydrogen ion concentration and carbon dioxide tension in ether anesthesia have been studied thoroughly by previous observers, and they will be considered here only in connection with the discussion on alterations in the cardiac output. Cullen, Austin, Kornblum, and Robinson [19] found that the larger part of the fall in alkali reserve that occurs with ether, chloroform and nitrous oxide anesthesia occurs during the first few minutes of the anesthesia. Their studies indicated that exertion and anoxemia alone were not responsible for the entire fall. The immediate fall in $p_H$ associated with the fall in

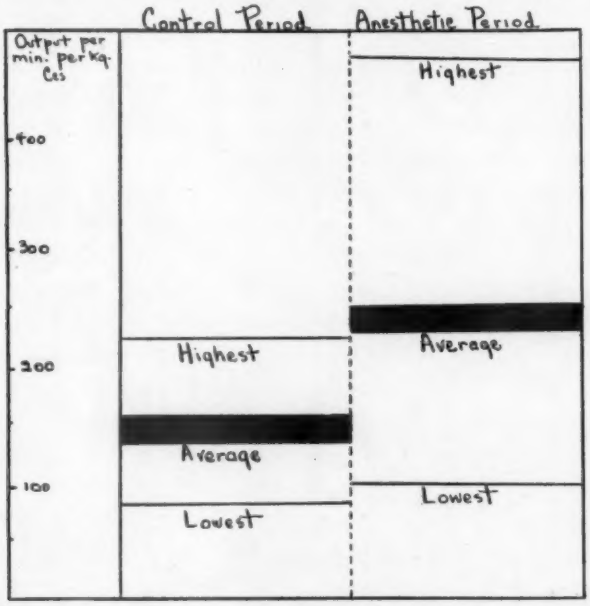


Chart 3.—This is a composite chart of all experiments with the exception of two (tables 14 and 17) in which there was a rather marked decrease in the cardiac output during profound ether anesthesia. The position of the thick black line for the control period was obtained by taking the average of twenty-eight determinations of the cardiac output, and that for ether anesthesia period by taking the average of twenty-three determinations. It is to be noted that the average figure for cardiac output during ether anesthesia is greater than the largest figure obtained during the control period.

alkali reserve led them to believe that the condition was that of an uncompensated acidosis and not that of a compensated alkalosis.

It is of interest to speculate as to the underlying agencies responsible for the increased cardiac output in ether anesthesia. Henderson [20] has

19. Cullen, G. E.; Austin, J. H.; Kornblum, K., and Robinson, H. W.: J. Biol. Chem. **56**:625 (June) 1923.

20. Henderson, Y.: Am. J. Physiol **21**:126, 1908; Physiol. Reviews **3**:165 (April) 1923.

TABLE 14.—*Effect of Ether Anesthesia on the Cardiac Output*

| Date | Weight, Kg. | Temperature, Fahrenheit | Pulse Rate per Minute | Arterial Oxygen, per Cent by Volume | Venous Oxygen, per Cent by Volume | Arteriovenous Difference, per Cent by Volume | Arterial Carbon Dioxide, per Cent by Volume | Venous Carbon Dioxide, per Cent by Volume | Oxygen Consumption, Cc. per Minute | Cardiac Output, Cc. per Minute | Output per Kg. per Minute, Cc. | Output per Beat, Cc. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 6/19/26, 12:10 p. m.: Control study; ¾ grain morphine.... | 9.7 | 100 | 68 | 22.42 | 12.64 | 9.78 | 36.61 | 42.17 | 73.8 | 755 | 78 | 11 |
| 1:45 p. m.: Second control study ..... | 9.7 | 102 | 48 | 22.54 | 13.12 | 9.42 | 37.12 | 43.12 | 73.8 | 783 | 81 | 16 |
| 2:50 p. m.: Very deep anesthesia for 35 minutes..... | 9.7 | 101 | 168 | 23.38 | 12.52 | 10.86 | 27.39 | 32.68 | 51.7 | 414 | 43 | 2.4 |
| 4:05 p. m.: Anesthesia for 35 minutes ..... | 9.7 | 101 | 160 | 23.14 | 17.65 | 5.49 | 23.32 | 26.71 | 73.8 | 1,344 | 139 | 8.4 |

Protocol: 6/19/26: At 11:30 a. m., ¾ grain of morphine was administered; at 12:10 p. m., control studies were made; at 1:45 p. m., second control studies were made; at 2:17 p. m., ether anesthesia was begun; at 2:50 p. m., animal was deeply under anesthetic, eye reflexes were abolished, stopped breathing just at time specimens of blood were drawn. Eye reflexes were present almost up to time animal stopped breathing. Animal revived. At 3:30 p. m., anesthetic was resumed; animal stopped breathing once, but eye reflexes were present at 4:00 p. m., when specimens of blood were taken. Animal well relaxed at time.

TABLE 15.—*Effect of Ether Anesthesia on the Cardiac Output*

| Date | Weight, Kg. | Temperature, Fahrenheit | Pulse Rate per Minute | Arterial Oxygen, per Cent by Volume | Venous Oxygen, per Cent by Volume | Arteriovenous Difference, per Cent by Volume | Arterial Carbon Dioxide, per Cent by Volume | Venous Carbon Dioxide, per Cent by Volume | Oxygen Capacity, per Cent by Volume | Oxygen Consumption, Cc. per Minute | Cardiac Output, Cc. per Minute | Output per Kg. per Minute, Cc. | Output per Beat, Cc. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 3/24/26: Control study; no morphine ..... | 18.1 | 102 | 150 | 23.4 | 16.83 | 6.57 | 41.32 | 46.30 | ..... | 151.3 | 2,308 | 127.2 | 15 |
| 6/21/26, 4:00 p. m.: Control study; no morphine..... | 17.8 | 102 | 120 | 19.27 | 12.96 | 6.31 | 35.64 | 39.42 | ..... | 160.7 | 2,689 | 151.1 | 22 |
| 6/21/26, 5:15 p. m.: After 40 minutes ether ..... | 17.8 | 102 | 175 | 9.86 | 6.42 | 3.46 | 35.10 | 38.07 | 21.22 (40%) | 118.1 | 3,413 | 192 | 19 |

Protocol: 3/24/26: Elderly trained dog; no morphine, control determinations. 6/21/26: At 4:00 p. m., control study was made, no morphine was given. At 4:25 p. m., ether anesthesia was begun. The eye reflexes were never abolished, but in an attempt to do so, marked cyanosis of the mucous membranes developed. Specimens of blood were taken forty-five minutes after the anesthetic was begun, with dog deeply anesthetized at the time.

ascribed great importance to carbon dioxide as a regulator of the cardiac output. Boothby [21] first suggested that hydrogen ion concentration regulated the output of the heart. Douglas and Haldane [22] were led to the same conclusion as a result of studies on man. Means [23] stated that he thought it likely that the hydrogen ion concentration regulated the output of the heart. Harrison, Wilson and Blalock [24] have shown that an increase in the hydrogen ion concentration is associated with an increased cardiac output, and that a decreased hydrogen ion concentration is associated with a decreased output. The administration of an ether anesthetic in the present studies was accompanied by an increase in the hydrogen ion concentration and usually by an increase in the cardiac output.

If the elevated hydrogen ion concentration is a factor in increasing the output of the heart in ether anesthesia, it is possible that it is due to the capillary dilatation which it causes. Fleisch [25] found that acid causes a peripheral dilatation, and that, other factors remaining the same, this results in a more rapid filling of the heart in diastole with an increased output. Eppinger [26] believes that the increase in the cardiac output during attacks of "cardiac asthma" is due to diminished peripheral resistance. The same interpretation is given by Harrison, Dock and Holman [27] in explaining the elevated output in dogs with arterio-venous fistulae. The experiments of Cattell [11] do not support the view that ether causes a peripheral dilatation. He stated:

> Determinations of leg volume with a plethysmograph, perfusion rate measurements, and results obtained by the injection of ether directly into the circulation, together with the form of blood pressure curves, indicate that ether causes a contraction of the peripheral vessels.

No observations on the peripheral circulation were made in this study.

Patterson [28] found that carbon dioxide alone depresses all of the functions of the isolated heart, but that the combined effect of carbon dioxide and epinephrine resulted in more rapid and stronger contractions and more rapid relaxation, and also lengthening of the diastolic filling. Cannon and Corrasco-Formiguera [29] stated that asphyxia increases the

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21. Boothby, W. M.: Am. J. Physiol. **37**:383, 1915.
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23. Means, J. H.: Dyspnoea, Medicine, **3**:309 (Aug.) 1924.
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TABLE 16.—*Effect of Ether Anesthesia on the Cardiac Output*

| Date | Weight, Kg. | Temperature, Fahrenheit | Pulse Rate per Minute | Arterial Oxygen, per Cent by Volume | Venous Oxygen, per Cent by Volume | Arteriovenous Difference, per Cent by Volume | Arterial Carbon Dioxide, per Cent by Volume | Venous Carbon Dioxide, per Cent by Volume | Oxygen Consumption, Cc. per Minute | Cardiac Output, Cc. per Minute | Output per Kg. per Minute, Cc. | Output per Beat, Cc. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 5/25/26, 8:15 a. m.: Control study | 10.5 | 102 | 90 | 19.16 | 13.55 | 5.61 | 34.46 | 37.72 | 103.3 | 1,841 | 175 | 20 |
| 5/25/26, 4 p. m.: After ether for 17 minutes | 10.5 | 102 | 215 | 20.60 | 16.69 | 3.91 | 24.44 | 28.08 | 99.6 | 2,547 | 242 | 12 |
| 5/26/26, 4 p. m.: Control study | 10.5 | 101.6 | 108 | 19.11 | 12.62 | 6.49 | ..... | ..... | 118.1 | 1,820 | 173 | 17 |

Protocol: 5/25/26: Healthy dog. At 8:15 a. m., control determinations were made without morphine. An attempt was then made to anesthetize the dog by giving ether and cotton seed oil per rectum. This was unsuccessful. At 3:45 p. m., ether by mask was given for seventeen minutes before specimens of blood were taken, eye reflexes being barely obtainable. 5/26, 4:00 p. m., control study without morphine.

TABLE 17.—*Effect of Ether Anesthesia on the Cardiac Output*

| Date | Weight, Kg. | Temperature, Fahrenheit | Pulse Rate per Minute | Arterial Oxygen, per Cent by Volume | Venous Oxygen, per Cent by Volume | Arteriovenous Difference, per Cent by Volume | Arterial Carbon Dioxide, per Cent by Volume | Venous Carbon Dioxide, per Cent by Volume | $p_H$ | Oxygen Consumption, Cc. per Minute | Cardiac Output, Cc. per Minute | Output per Kg. per Minute, Cc. | Output per Beat, Cc. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 6/26/26, 5 p. m.: Control study; ½ grain morphine | 11 | 99 | 48 | 16.89 | 11.65 | 5.24 | 41.18 | 44.15 | 7.35 | 70.1 | 1,338 | 122 | 28 |
| 6/26/26, 5:50 p. m.: After ether for 15 minutes | 11 | 98.6 | 155 | 17.25 | 10.11 | 7.14 | 34.43 | 39.56 | 7.27 | 62.7 | 877 | 80 | 5.7 |
| 6/27/26, 3 p. m.: After ether for 25 minutes | 11 | 98 | 160 | 12.72 | 6.42 | 6.30 | 29.75 | 36.05 | 7.25 | 77.5 | 1,230 | 112 | 7.7 |

Protocol: 6/26/26: At 4:00 p. m., ½ grain of morphine was given. At 5:00 p. m., control study was made. No food had been taken for previous twenty-four hours. At 5:35 p. m., ether anesthesia was begun. At 5:50 p. m., determinations were made, eye reflexes being abolished completely; mucous membranes were rather blue in color.

6/27/26: At 2:40 p. m., ether anesthesia was begun. At 3:00 p. m., determinations were made, eye reflexes being abolished completely.

secretion of epinephrine, but Kodama [30] found in his experiments on dogs that ether anesthesia decreases the rate of epinephrine output from the suprarenal glands. Corbett [31] reported a decrease in the epinephrine content of the suprarenal glands in ether anesthesia. In view of these observations, it does not seem plausible to assume that the increased cardiac output during ether anesthesia is associated with changes in the epinephrine content of the blood.

Cullen, Austin, Kornblum and Robinson [19] found an increased oxygen unsaturation of the blood during ether anesthesia. Bloch [32] studied the effect of ether anesthesia on the hemoglobin and red blood cells, and stated that prolonged anesthesia causes degeneration of the red blood cells with the resulting escape of hemoglobin. Harrison and Blalock [33] have found that severe anoxemia causes a marked increase in the cardiac output. The percentage saturation of the arterial blood was decreased in several of the present experiments, and this factor probably plays a part in the increased output of the heart. Since the ether anesthetics were not always associated with a decrease in the percentage saturation, it is thought that all of the change cannot be ascribed to anoxemia.

Part of the increase in the cardiac output during ether anesthesia might possibly be due to the increased respiratory effort during the early stages of the anesthetic. If this change were due entirely to the elevated metabolism of increased work, a parallelism between oxygen consumption and blood flow would be expected. The oxygen consumption usually decreased during ether anesthesia, and the body temperature was lowered by prolonged anesthesia. Yamakita,[34] studying the cerebral blood flow and oxygen consumption in ether anesthesia, found an increase in the stage of excitation, a decrease (over 50 per cent) during the narcosis and an increase after it. In the present report, the increased output of the heart was due to the lessening of the coefficient of utilization (figs. 1 and 2) without any increase in the oxygen consumption.

It is possible that the mechanical effects of changes in the depth of the respiratory movements might cause variations in the venous inflow with a resultant action on the cardiac output. This is improbable, since Marshall [35] has found that the cardiac output of the normal dog is no greater in summer than in winter, although the minute ventilation may be doubled by panting.

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33. Harrison, T. R., and Blalock, A.: Unpublished observations.
34. Yamakita, M.: Tohoku J. Exper. Med. **3**:414 (Dec.) 1922.
35. Marshall, E. K.: Personal communication, 1925.

TABLE 18.—*Effect of Ether Anesthesia on the Cardiac Output*

| Date | Weight, Kg. | Temperature, Fahrenheit | Pulse Rate per Minute | Arterial Oxygen, per Cent by Volume | Venous Oxygen, per Cent by Volume | Arteriovenous Difference, per Cent by Volume | Arterial Carbon Dioxide, per Cent by Volume | Venous Carbon Dioxide, per Cent by Volume | $p_H$ | Oxygen Consumption, Cc. per Minute | Cardiac Output, Cc. per Minute | Output per Kg. per Minute, Cc. | Output per Beat, Cc. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 6/28/26, 3 p. m.: Control study; 1 grain morphine... | 13.3 | 99.4 | 50 | 15.58 | 10.11 | 5.47 | 35.78 | 40.37 | 7.42 | 87.66 | 1,603 | 120 | 32 |
| 3:55 p. m.: After 15 minutes anesthesia ..... | 13.3 | 99 | 120 | 15.58 | 12.72 | 2.86 | 35.37 | 37.53 | $7.37_6$ | 78.41 | 2,742 | 206 | 23 |

Protocol: 6/28/26: At 2:00 p. m., 1 grain of morphine was given. At 3:20 p. m., control specimens of blood were drawn; animal was quiet. At 3:40 p. m., ether anesthetic was begun. Determinations were made fifteen minutes later, eye reflexes being abolished completely

TABLE 19.—*Effect of Ether Anesthesia on the Cardiac Output*

| Date | Weight, Kg. | Temperature, Fahrenheit | Pulse Rate per Minute | Arterial Oxygen, per Cent by Volume | Venous Oxygen, per Cent by Volume | Arteriovenous Difference, per Cent by Volume | Arterial Carbon Dioxide, per Cent by Volume | Venous Carbon Dioxide, per Cent by Volume | Oxygen Consumption, Cc. per Minute | Cardiac Output, Cc. per Minute | Output per Kg. per Minute, Cc. | Output per Beat, Cc. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 7/19/26, 3 p. m.: Control study; ¾ grain morphine..... | 13.5 | 102 | 60 | 8.46 | 3.90 | 4.56 | 39.16 | 42.64 | 97.2 | 2,132 | 158 | 35.5 |
| 7/19/26, 3:50 p. m.: After ether for 35 minutes ..... | 13.5 | 101.6 | 120 | 8.72 | 6.27 | 2.45 | 39.02 | 42.24 | 86.4 | 3,527 | 266 | 29.3 |

Protocol: 7/19/26: At 2:00 p. m., ¾ grain of morphine was given. At 3:00 p. m., animal was quiet, and control determinations were made. At 3:15 p. m., giving of ether anesthetic was begun. Specimens of blood were drawn at 3:50 p. m., after thirty-five minutes of anesthesia, eye reflexes being abolished at times.

The figures obtained for the oxygen capacity of the arterial blood indicate that an anemia was not produced by the anesthetic. Hence, any effect which anemia exerts on the cardiac output can be ruled out in these experiments.

The possible clinical significance of the increase in the cardiac output during ether anesthesia will be considered in subsequent papers.

## SUMMARY AND CONCLUSIONS

The cardiac output of the heart of the dog during ether anesthesia has been studied by the Fick method. Six experiments were performed on trained animals, and thirteen on dogs to which morphine had been given. The cardiac output of the heart was increased (from 7 to 180 per cent) in all instances except three. These three animals were deeply anesthetized at the time of the determinations. The changes in pulse rate, temperature readings, oxygen consumption, arterial oxygen, venous oxygen, arterial carbon dioxide, venus carbon dioxide, hydrogen ion concentration and cardiac output have been observed. The following statements are true for the dog, and may possibly be true for man.

1. Ether anesthesia causes an increased cardiac output (average increase 76 per cent).

2. The output of the heart is less than normal only when the degree of anesthesia is profound.

3. The increased cardiac output is not associated with an increased oxygen consumption, but is associated with a diminution in the oxygen coefficient of utilization.

4. This change is associated with an increase in the hydrogen ion concentration of the blood, with a decrease in the carbon dioxide content of the blood, and may or may not be accompanied by a diminution in the percentage saturation of the arterial blood.

# EXPERIMENTAL CHRONIC DUODENAL OBSTRUCTION

## I. TECHNIC AND PHYSIOLOGY *

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There is a growing tendency on the part of clinicians to believe that many obscure and indefinite symptoms are due to the absorption of toxins from the intestinal tract. It is on this hypothesis that high colonic irrigations, bacterial implantations, etc., have been recommended in certain diseases. In addition, some of the more serious conditions, such as pernicious anemia, have been attributed to intestinal intoxication. Though the belief that these hypothetical toxins are produced in the intestinal tract has been prevalent for years, little direct evidence has been brought forward to support the idea. It was in the hope that we might learn something more definite that the following experiments were conducted.

Since the symptoms and diseases that have been attributed to the absorption of toxins from the intestinal tract are characterized by their chronicity, we produced and studied experimental lesions existing for a prolonged period. In our first study [1] we endeavored to confirm the observations of Pawlow and his co-workers,[2] Fischler [3] and others, that dogs with Eck fistulas, kept on an exclusive meat diet, developed symptoms of intoxication. However, in a series of dogs with Eck fistulas which we kept on a similar diet, no such symptoms were observed. It was concluded from these experiments that the occurrence of symptoms was too irregular for systematic study. In addition, the liver function of these dogs was tested according to the dye method described by Rosenthal.[4] Our results indicated that there was no impair-

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1. Berg, B. N.; Cone, W. V., and Jobling, J. W.: Phenoltetrachlorphthalein Test of Liver Function in Eck Fistula Dogs Kept Upon a Meat Diet, Proc. Soc. Exper. Biol. and Med. **23**:81, 1925.

2. Hahn, M.; Massen, O.; Nencki, M., and Pawlow, J.: Die Eck'sche Fistel zwischen der unteren hohlvene und der Pfortader und ihre Folgen für den Organismus, Arch. f. Exper. Path. u. Pharmakol. **32**:161 (Sept. 11) 1893.

3. Fischler, F.: Uber die Fleischintoxikation bei Tieren mit Eck'scher Fistel, Deutsche Arch. f. Klin. Med. **104**:300 (Nov. 7) 1911.

4. Rosenthal, S. M.: An Improved Method for Using Phenoltetrachlorphthalein as a Liver Function Test, J. Pharmacol. & Exper. Therap. **19**:385 (June) 1922.

ment in the ability of the liver to remove the disodium salt of phenoltetrachlorphthalein from the blood stream, although the liver showed the characteristic atrophic and fatty changes that occur following the establishment of an Eck fistula. Subsequently, Mann and Bollman [5] demonstrated that even large sections of a liver in which an Eck fistula had been established were resected, the elimination of the dye remained within relatively normal limits.

The present series of experiments includes a study of the effects of prolonged stasis in the duodenum, a part of the intestinal tract that is characterized normally by its rapid motility and relative freedom from bacteria. The first two papers of this series deal with the technic, physiology and bacteriology of experimental chronic duodenal obstruction.

During the last few years, numerous clinical observations have been made concerning the relationship between duodenal stasis and systemic disease. A clinical syndrome due to chronic duodenal ileus has been described, and relief of symptoms has been obtained by releasing the mechanical obstruction.[6] A marked increase in the bacterial content of the duodenum has been noted in cases of pernicious anemia, inflammatory diseases of the biliary tract and various gastric disturbances.[7] Chronic intestinal obstruction has been found to coexist with some cases of pernicious anemia. An important rôle in the genesis of this disease has been ascribed to the absorption of hematoxins from the intestine associated with a marked increase in the number of bacteria of the small intestine.[8] Brown and his co-workers [9] have described a toxic nephritis associated with "duodenal toxemia."

Nothing has appeared in the literature concerning the experimental production of chronic duodenal obstruction, except the work of Koennecke and Meyer.[10] These authors believed that chronic duodenal

5. Mann, F. C., and Bollman, J. L.: An Experimental Study of Reduced Hepatic Function, Am. J. Physiol. **76**:179 (March) 1926; Liver Function Tests, Arch. Path. & Lab. Med. **1**:681 (May) 1926.

6. Higgins, C. C.: Chronic Duodenal Ileus with Report of Fifty-Six Cases, Arch. Surg. **13**:1 (July) 1926.

7. Olivet, J.: Bakteriologie des Duodenums, Klin. Wchnschr. **5**:307 (Feb. 19) 1926. Löwenberg, W.: Pathologische Bakterienansiedlung im Duodenum und ihre Ursächlichen Faktoren, Klin. Wchnschr. **5**:548 (March 26) 1926.

8. Seyderhelm, R.: Die Bedeutung des Dünndarms für die Genese der Perniziösen Anämie, Klin. Wchnschr. **3**:568 (April 1) 1924. Seyderhelm, R.; Lehmen, W., and Wichels, P.: Experimentelle Intestinale Perniziöse Anämie beim Hund, Klin. Wchnschr. **3**:1439 (Aug. 5) 1924.

9. Brown, G. E.; Eusterman, G. B.; Hartman, H. R., and Rowntree, L. G.: Toxic Nephritis in Pyloric and Duodenal Obstruction, Arch. Int. Med. **32**:425 (Sept.) 1923.

10. Koennecke, W., and Meyer, H.: Klinisches und Experimentelles zur Chronischen Duodenalstenose, Deutsche Ztschr. f. Chir. **175**:179 (Sept.) 1922.

ileus in man was due to mechanical pressure at the duodenojejunal flexure, and reproduced the condition in dogs by narrowing the lumen of the duodenum with a free, narrow strip of fascia. They fixed the duodenum to the costal arch at the site of the obstruction.

In order to produce conditions that were favorable for the study of the effects of prolonged duodenal stasis in dogs, a method was employed which we subsequently learned was similar to that adopted by Koennecke and Meyer in their work. We believe, however, that our method has the following advantages: By the use of a wide fascial flap attached by a broad pedicle to the posterior sheath of the rectus muscle, instead of a free, narrow, fascial strip, the blood supply of the obstructing band is insured; the obstruction lasts longer, and the danger of the band cutting through the intestine is diminished.

## TECHNIC

Under ether anesthesia and with strict asepsis, a right rectus muscle-splitting incision is made. The posterior sheath, including the parietal peritoneum is incised close to the midline, and a rectangular fascial flap, about 4.5 by 6 cm., is made; usually some of the transversalis muscle is included. The size of the flap varies with the diameter of the duodenum. The latter is mobilized, and a segment about 15 cm. from the pylorus is chosen for the site of the obstruction, which varies with the length of the duodenum. An incision equal in size to the width of the flap is made in the mesentery close to the attachment of the duodenum. The flap is pulled through this opening, and five mattress sutures are introduced at the margin and near the base. The distance between the two limbs of the sutures is approximately one and one-half times the diameter of the duodenum. As the sutures are tightened, a closed forceps is introduced between them and the intestine, in order to avoid interference with the blood supply. If at a succeeding exploratory operation the obstruction is deemed inadequate, the fascial band can be tightened by taking a reef in it, a series of interrupted sutures being used. The peritoneum and fascia are closed by a continuous suture and the skin by a subcuticular suture. Silk is used throughout. For the first few days after the establishment of the obstruction, the dogs are kept on a fluid diet after which they are given a liberal amount of cooked chopped meat, bread and bone ash.

## EXPERIMENTAL RESULTS

The foregoing method of producing a chronic duodenal obstruction in the dog was successful in twelve of fifteen attempts. Partial occlusion of the duodenum at the site of the obstruction, and dilatation and hypertrophy proximal to the obstruction were found at exploratory laparotomy and at autopsy.

While it was difficult to determine accurately the amount of dilatation due to changes in the tonus of the duodenum, it was found convenient, for tabulation and discussion, to adopt, as a rough measure, the notation given in the accompanying table.

The effects of the partial obstruction on the segment of the duodenum proximal to it as shown in the accompanying table, varied in the different animals. At exploratory operation, in seven dogs a three or four plus dilatation was found from sixty-three to one hundred and twenty-one days after the establishment of the obstruction; in five dogs, a two plus dilatation was present in from thirty-five to one hundred and nineteen days.

Some of the dogs vomited during the first twenty-four hours after the operation. For the first few days, they ate little food. Subsequently, none of them exhibited any objective symptoms except occasional vomiting. Seven dogs lived for periods varying from fifty-nine to 190 days after the obstruction was established. Shortly before death, five developed symptoms of acute ileus; two were killed. Of the seven dogs in this series, four became emaciated. The remaining five are alive, and had been under observation for from 174 to 240 days on September 15.

*Degrees of Dilatation After Obstruction**

| Number of Dog | First Exploratory Operation; Days after Obstruction | Degree of Dilatation | Second Exploratory Operation; Days after Obstruction | Degree of Dilatation | Third Exploratory Operation; Days after Obstruction | Degree of Dilatation | Autopsy; Days after Obstruction |
|---|---|---|---|---|---|---|---|
| 8190 | 17 | + | 81 T | ++ | 119 | +++ | 190 |
| 8191 | 17 | ++++ | 77 | ++++ | 121 | ++++ | ... |
| 8209 | 10 | + | 70 T | ++ | 119 | ++ | ... |
| 8295 | 39 | ++ | 108 | ++ | ... | .. | 113 |
| 8313 | 35 T | ++ | .. | .. | ... | .. | 73 |
| 8314 | 35 | +++ | 80 | +++ | ... | .. | ... |
| 8332 | 49 T | ++ | 70 | +++ | ... | .. | ... |
| 8360 | 49 T | ++ | .. | .. | ... | .. | 59 |
| 8361 | 45 T | ++ | 80 | +++ | ... | .. | 151 |
| 8364 | 45 | ++ | 79 | +++ | ... | .. | 161 |
| 8417 | 30 | ++++ | 63 | ++++ | ... | .. | 84 |
| 8418 | 32 T | + | 66 | ++ | ... | .. | ... |

* In the table, + represents slight dilatation; ++, moderate dilatation (less than twice the normal diameter); +++, marked dilatation (about twice the normal diameter), and ++++, extreme dilatation (more than twice the normal diameter); T, fascial band tightened at this operation.

The nutrition of these dogs remains unimpaired. No abnormalities of the stools were observed. Complete autopsy observations will be included in a later report.

## PHYSIOLOGY

The fluoroscopic observations in clinical cases of duodenal obstruction have been described by Jordan,[11] Wheelon,[12] Koennecke and Meyer,[10] Ratkoćzi[13] and others. In general, they found stasis and reverse motility in the duodenum, gastric and duodenal hyperperistalsis,

11. Jordan, A. C.: The Duodenum and the Appendix in Intestinal Stasis, Brit. M. J. **1**:1225 (June 1) 1912.

12. Wheelon, H.: Observations on Gastric and Duodenal Motility in Duodenal Obstruction, J. A. M. A. **77**:1404 (Oct. 29) 1921.

13. Ratkoćzi, N.: Chronic Stenosis of Duodenum, Am. J. Roentgenol. **12**: 246 (Sept.) 1924.

pyloric insufficiency and reflux into the stomach. Ratkoćzi's description of so-called chronic "intermittent stenosis" of the duodenum contained many features comparable to some of our experimental observations.

In experimental obstruction of the duodenum, the only reports of fluoroscopic examinations that we found recorded were those of Koennecke and Meyer,[10] who correlated their clinical with their experimental observations. They stressed the hypermotility of the stomach and duodenum in the presence of experimental stenosis and noted that section of the vagus had only a transitory effect on gastric tonus after the obstruction had been established for a prolonged period. Occasionally, they identified deep peristaltic waves which originated in the stomach and progressed over the duodenum in contrast to the to-and-fro movements of the duodenum. However, they did not recognize any rhythmic relation between antral, pyloric and duodenal activity.

## METHOD

In order to study the degree of stasis and alterations in the peristaltic activity of the stomach and the duodenum in the presence of a prolonged subacute obstruction of the latter, fluoroscopic examinations were made with the aid of an opaque meal. Seven dogs were examined. Three separate series of observations were made on each dog, with intervals of from one to two weeks between each examination. The obstructions had existed from 115 to 173 days when the first fluoroscopic observations were made. Eight ounces of a suspension of barium sulphate was given to the dogs by stomach tube. They received no food eighteen hours before the examination. Observations were made in the following manner: immediately, at the end of one hour, two hours, three and one-half hours, and five hours (in only two series). The fixation of the duodenum to the anterior abdominal wall facilitated accurate study, and the site of the obstruction was readily recognized. There was no evidence of kinking below the obstruction.

## MOTILITY

In the normal dog, fluoroscopic examination is unsatisfactory for the observation of the motor relationship between the duodenum, pyloric sphincter and antrum. However, in the presence of an obstruction of the duodenum, we found that the accentuation of the contractions and the delayed motility enabled us to distinguish, simultaneously, the activity of each. We observed a cycle that was suggestive of one described by Wheelon and Thomas [14] in the normal dog, but which differed in certain respects.

As soon as enough barium had passed through the pylorus, the duodenum appeared as a long, sausage-shaped structure, limited above by the pyloric sphincter and below by the obstruction. The degree of dilatation varied; in some dogs the duodenum was many times its normal

14. Wheelon, H., and Thomas, J. E.: Observations on the Motility of the Duodenum and the Relation of Duodenal Activity to that of the Pars Pylorica, Am. J. Physiol. **59**:72 (Feb.) 1922.

size; in others, the dilatation was less pronounced. Variations also occurred in the same dog at different observations. These changes were probably the result of alterations in tonus; because of this it was considered futile to compare roentgenographic appearances with gross dilatation observed at exploration. However, there seemed to be some correlation between the latter and the degree of stasis. This is discussed in detail under the heading of stasis and dilatation.

After the filling of the duodenum, the following cycle was observed in six of the seven dogs that were examined: A deep peristaltic contraction appeared in the antrum and progressed toward the pylorus; sometimes the entire antrum appeared to contract at one time instead of in the form of a peristaltic wave. As the wave approached the pylorus, the latter opened and barium passed through into the duodenum; then the pylorus closed, and the contraction traversed the duodenum, causing a marked bulge in the latter as it approached the obstruction. Immediately after this there appeared a definite to-and-fro motion of the mass of barium in the duodenum (apparently independent of the antrum), the result of deep contractions that traveled alternately toward the obstruction and then toward the pylorus. During reverse movements, the bulb was momentarily distended, especially when the sphincter was closed. At some observations, the sphincter was open, and reflux into the antrum occurred. After four or five of these alternating contractions, peristaltic activity in the antrum appeared anew, and the rhythmic cycle was repeated. In the interval between contractions, the antrum appeared to be inactive and usually only partly filled with barium. Sometimes it was empty, possibly because of a tonic contraction of the so-called "sphincter antri pylorici" [15] or of the antrum itself. Similarly, the duodenum at times did not contain barium; this may have been caused by a tonic contraction of either the pyloric sphincter or of the duodenum. In such cases, the cycle could not be distinguished. In one dog, in which there was apparently slight obstruction, the cycle was not observed. It will be noticed throughout the remainder of the study that this dog was practically normal.

Sometimes, when the lower or middle portion of the duodenum was tonically contracted, the cycle could be identified only in the upper duodenum and bulb. When reflux into the antrum was marked, the duodenum and antrum appeared to be continuous, and it was more difficult to distinguish the cycle. It seemed as though the antral peristaltic wave spent itself more rapidly than usual, because of increased resistance from irregular contractions in the duodenum. At many observations, the barium was propelled beyond the obstruction in jets, which followed only duodenal contractions of antral origin. At other times,

15. Hofmeister, F., and Schütz, E.: Uber die Antomatischen Bewegungen des Magens, Arch. f. Exper. Path. u. Pharmakol. **20**:1 (Oct. 6) 1886.

the barium appeared below the obstruction in a continuous thin stream, throughout the cycle.

When the antrum and duodenum were well outlined, the rhythmic motor activity described above was recognized with few exceptions at the immediate, the one-hour and the two-hour observations and less often at the end of three and one-half hours. At the five-hour period, the duodenum usually appeared flaccid and dilated, and was traversed by feeble, irregular contractions. Occasionally, moderately deep alternating contractions persisted. No barium was observed passing the site of the obstruction at this time. This may have been because of the fact that the amount propelled beyond the obstruction was too small to be detected fluoroscopically.

The body and fundus of the stomach were often separated from the antrum by a deep contraction band. The antrum maintained a regular rhythm, which seemed to be independent of activity in the cardiac portion of the stomach. In the latter, peristalsis appeared in the form of "ripples," although occasionally, when the waves were sufficiently deep, they were observed traversing the antrum. As a rule, however, they were too shallow for any relationship between them and the antral contractions to be disclosed fluoroscopically.

## COMMENT

According to Wheelon and Thomas,[14] a rhythmic cycle that follows the "law of the intestine" [16] exists between the antrum, pyloric sphincter and the duodenum. In the normal dog, as soon as the antral peristaltic wave has reached the sphincter, the antrum begins to relax and remains relaxed during the sphincteric and duodenal contractions. The cycle terminates with the reappearance of an antral contraction. Similarly, in chronic duodenal obstruction there was a positive and negative phase of antral activity. Immediately after the wave of contraction passed from the antrum to the sphincter and duodenum, the antrum relaxed and remained inactive during four or five independent secondary contractions in the duodenum. The cycle ended with the reappearance of an antral contraction. However, the duodenum appeared to contract continuously without a phase of relaxation which corresponded to that of the antrum. In the latter, the negative phase seemed to be prolonged and the rate of rhythmic contraction slow.

The accentuated contractions and the reverse motility of the duodenum were due, probably, to changes in tonus associated with the dilatation and to abnormal stimuli arising at the obstruction. The irregular activity of the duodenum represented either exaggerated segmental contractions [14] or independent peristaltic and retroperistaltic waves. The

16. Bayliss, W. M., and Starling, E. H.: The Movements and Innervation of the Small Intestine, J. Physiol. **24**:99 (May 11) 1899.

delayed motility, especially at the five-hour observation, may be explained by alterations in the "gradient," as described by Alvarez.[17]

The tonicity of the pyloric sphincter varied during the phase of independent duodenal activity. At some observations, it appeared contracted; at others, it allowed reflux into the antrum. The activity of the sphincter can be modified by duodenal motility during the negative phase of the antrum.[14] The prolonged reverse motility of the obstructed duodenum probably induced marked alterations in the pyloric sphincter, which, however, were not recognized by the fluoroscope.

The site of origin of the antral peristaltic contraction, which appeared to be independent of activity in the fundus and body of the stomach, requires finer methods of study for a more accurate interpretation. Recently, Klein[18] found that, normally, antral contradictions may originate either at a nodal center near the cardia, along the lesser curvature of the stomach, or independently, at a separate nodal center at the reentrant angle.

### STASIS

In all of the dogs, there was a delay in the passage of the barium through the duodenum proximal to the site of the obstruction. The emptying time and the amount of residue varied. In four dogs, there was a persistent residue at the end of five hours; in two dogs, the duodenum was filled with barium at one five-hour observation, but was empty at another. In one dog, the duodenum was always empty at the one-hour observation. This dog was referred to earlier as having practically no delay in motility.

More pronounced variations occurred in the emptying time of the stomach. However, marked irregularities also exist normally. At one observation of a normal, fasting dog, the stomach was empty at the end of one hour; at another observation of the same dog, a gastric residue was still present at the end of three hours. Wheelon and Thomas[14] noted similar variations in the dog and in man. Bloomfield and Keefer,[19] employing a different method, recently reported wide differences in the motility of the normal stomach in man.

In chronic duodenal obstruction, the stomach always contained barium at the one-hour observation, except in the dog in which the obstruction apparently had little effect. In one series, four dogs had five-hour gastric residues. In another series none of the dogs had

17. Alvarez, W. C.: The Mechanics of the Digestive Tract, New York, Paul B. Hoeber, Inc., 1922.

18. Klein, E.: Gastric Motility: Origin and Character of Gastric Peristalsis, Arch. Surg. **12**:571 (Feb.) 1926.

19. Bloomfield, A. L., and Keefer, C. S.: Clinical Physiology of the Stomach: Simultaneous Quantitative Observations on Gastric Secretory Volume, Acidity and Motility, Arch. Int. Med. **38**:145 (Aug.) 1926.

residues at the end of five hours. It was interesting to note that, in the latter series, six dogs had marked stasis in the duodenum.

The pylorus usually allowed the passage of barium from the stomach to the duodenum at the immediate observation. Sometimes from five to fifteen minutes elapsed before any barium appeared in the duodenum. At the obstruction, after a short delay, barium usually began to enter the distal duodenum and the upper jejunum in varying amounts. However, in two dogs there was a marked delay of one-half hour and two hours, respectively. The latter dog developed symptoms of acute ileus the day after this observation. At the five-hour observation, except for the duodenal and gastric residues noted, the barium was in the large intestine and occasionally in the lower ileum also.

In one dog, the outline of a large oval mass was observed in the greatly dilated duodenum just above the site of the obstruction. It was in the same situation at the three series of observations. However, it did not obstruct the lumen of the duodenum completely, the barium passing around it in a thin film. The mass was probably a large hair ball (a similar one was found in the dilated duodenum of another dog that came to autopsy). This dog is in excellent condition and has evidenced no obstructive symptoms up to the present time.

### STASIS AND DILATATION

In spite of the fact that the fluoroscopic examinations were started from forty-two to sixty-four days after the last exploratory operation, the notes made at the explorations concerning the degree of dilatation of the duodenum coincided well with the degree of stasis observed roentgenologically. In five dogs, in which a marked dilatation of the duodenum (three or four plus) had been noted, a corresponding five-hour residue existed. In one dog, although only a moderate dilatation (two plus) had been observed, barium was still present in the duodenum at the end of five hours. This was the dog that had the mass in the duodenum described above; the added obstruction probably developed after the last exploratory investigation. In the other dog in which only a moderate dilatation had been observed (two plus), the duodenum was empty at the end of one hour.

Too much emphasis must not be placed on such observations, however, because the degree of stasis varies and is determined by many other factors besides the mere gross dilatation of the duodenum; the degree of the obstruction, the amount of compensatory hypertrophy and tonus of the duodenal musculature, the tonus of the pyloric sphincter, gastric motility, psychic factors, and the character of the food must all be considered. It is unfortunate that earlier fluoroscopic examinations were not made for comparative studies. Koennecke and Meyer [10] noted a five-hour residue in the duodenum of a dog in which the obstruction had existed five weeks.

## COMMENT

It is interesting to note that, despite active reverse motility in the duodenum, often with an open pylorus, vomiting occurred only twice during the fluoroscopic examinations, and infrequently during the entire period of observation. The symptoms associated with retention and reverse motility in the duodenum have been discussed from a clinical point of view by Wheelon [20] and others. In a series of seventy-four cases reported by Wheelon, only eight presented a history of vomiting. Clinically, chronic duodenal ileus is characterized by many subjective symptoms such as headache, dizziness, nausea, "biliousness," and a sense of fulness in the epigastrium.

However, since such subjective symptoms cannot be elicited experimentally, it is impossible to draw any analogies. None of the dogs developed the objective nervous symptoms usually associated with intoxication.

In view of the marked alterations in the duodenum associated with chronic obstruction, the possible relationship of such changes to infections of the biliary tract and alterations in the regulation of the flow of bile must be considered. Carlson,[21] Burget [22] and Kodama [23] have emphasized the possible importance of the tonus of the duodenal musculature in the closure of the ampullar end of the common duct. Preliminary studies of the dogs of this series indicate that the gallbladder bile in more than 50 per cent contained large numbers of organisms of intestinal origin.

## CONCLUSIONS

1. A simple method of producing chronic duodenal obstruction in the dog is described.

2. Dilatation and hypertrophy of the duodenum developed above the obstruction.

3. Fluoroscopic examinations confirmed the existence of prolonged duodenal stasis.

4. Alterations in the contractions of the antrum, the pyloric sphincter and the duodenum occurred, and a rhythmic cycle between the three was observed.

5. Except for emaciation in some of the dogs and occasional vomiting, there were no symptoms of intoxication.

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20. Wheelon, H.: Symptoms Associated with Duodenal Retention and Reverse Motility, J. A. M. A. **86**:326 (Jan. 30) 1926.

21. Carlson, A. J.: Physiology of the Liver, J. A. M. A. **85**:1468 (Nov. 7) 1925.

22. Burget, G. E.: The Regulation of the Flow of Bile, Am. J. Physiol. **74**: 583 (Nov.) 1925.

23. Kodama, S.: A Model to Simulate the Mechanism of Emptying of the Gallbladder, Am. J. Physiol. **77**:385 (July) 1926.

# EXPERIMENTAL CHRONIC DUODENAL OBSTRUCTION

## II. BACTERIOLOGY *

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In the search for a possible origin of some of the chronic and subacute illnesses of men in which there seems to be clinical evidence of a low grade intoxication, attention has recently been focused on the gastro-intestinal tract. In a previous paper, two of us with Cone [1] reported the failure to obtain evidence of absorption of toxic substances from the normal intestine in dogs that had Eck fistulas and that were kept on a meat diet. We were then led to study the effect after a partial obstruction of the intestine. It became evident at once that it would be necessary, before going further, to study the altered anatomy and physiology as well as the changes in the bacterial content of the intestine resulting from this procedure. In the paper immediately preceding this,[2] we have endeavored to indicate certain of the anatomic and physiologic alterations. In the present paper we shall present our observations with regard to the bacteriologic changes.

### HISTORICAL

Ever since Billroth [3] made the observation that the meconium of new-born babes was free from bacteria, and that micro-organisms made their appearance in the first yellow stools, bacteriologists and clinicians have been interested in the bacterial content of the intestine. Their interest has led to extensive researches to determine, if possible, the significance of the countless organisms which grow in the alimentary canal of animals and man. Their behavior during the normal physiologic

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1. Berg, B. N.; Cone, W. V., and Jobling, J. W.: Phenoltetrachlorphthalein Test of Liver Function in Eck Fistula Dogs Kept upon a Meat Diet, Proc. Soc. Exper. Biol. and Med. **23**:81, 1925.

2. Berg, B. N.; Meleney, F. L., and Jobling, J. W.: Experimental Chronic Duodenal Obstruction. I. Technic and Physiology, Arch. Surg.

3. Billroth, T.: Untersuchungen über Vegetationsformen von Coccobacteria Septica, Ser. 94, Berlin, 1874. (Quoted by Cushing and Livingood: Johns Hopkins Hosp. Rep. **9**:543, 1900).

function of the digestive tract is doubtless the outcome of age-long mutual adaptation which has resulted in the establishment of a relative equilibrium. The host survives with comparatively little evidence of injury to itself, and the bacteria maintain their species with relatively unimportant variation in numbers. Studies of this so-called normal relationship are interesting, but the disease phenomena which result from the invasion of the body by these bacteria after injuries to or the absorption of their products following altered physiologic processes of the alimentary canal makes fascinating problems for research.

Surgeons observed long ago that wounds of the stomach and upper intestine were not always followed by peritonitis as were wounds of the lower intestine. They found that operations in the upper regions could be performed with impunity, while sections of the lower portions were attended with grave risk of death. On the other hand, occlusions of the intestine produced profound symptoms of intoxication which were greater and more rapidly fatal when they were in the upper levels than when they were lower down. Cushing and Livingood,[4] were stimulated by the former observations to attempt a study of the bacteria from the human stomach, duodenum and jejunum, taking specimens as opportunity afforded at the time of or after operations on the alimentary canal and from fecal fistulas, for the most part in pathologic conditions. They also studied the intestinal fluid at various levels in rabbits and dogs. Old as it is, their work has many points of interest in the present discussion, and reference to it merits some detail. They were struck by the irregularity of their results, and concluded that there were no peculiar or stable flora in the intestine except perhaps *Bacillus coli* in the lower intestine. They found "no marked differences between the colonies on aerobic and anaerobic plates" but frequently saw bacteria in smears, which they could not cultivate. They confirmed the observations of previous research workers that there were many more bacteria in the lower than in the upper intestine. They noted, however, that the number at all levels decreased greatly after starvation, and that the lower limb of a fecal fistula became sterile. They concluded that bacteria were ingested with food and water and were killed in large numbers in the stomach if the food were delayed there for a time. Viable bacteria were therefore scanty in the duodenum but multiplied rapidly during their passage through the small intestine. After the passage of the chyme, if no more food was taken, the intestine tended to become amicrobic. They recommended the abstinence from food preliminary to operations

4. Cushing, H., and Livingood, L. E.: Experimental and Surgical Notes upon the Bacteriology of the Upper Portion of the Alimentary Canal, with Observations on the Establishment There of an Amicrobic State as a Preliminary to Operative Procedures on the Stomach and Small Intestine, Johns Hopkins Hospital Rep. **9**:543, 1900.

on the stomach and duodenum and presented cases to prove that the suggestion was a worthy one.

Since the publication of these observations, a number of authors have reported work which confirms many of the observations of Cushing and Livingood. The duodenal bucket has afforded to many observers, Libert,[5] Hoefer[6] and others, the opportunity to study the bacteria of the duodenum under normal and disease conditions. There is general uniformity of opinion that bacteria are found in the upper intestine in relatively small numbers under normal conditions of the stomach and biliary tract, but that the organisms in the mouth and pharynx and those contaminating the food and drink are found in great numbers if the gastric acidity is low, or if the biliary tract is diseased. In 1918 and 1919, Kendall,[7] and Torrey,[8] and others since that time, found that changes in diet modify the flora of the intestine, certain types of bacteria being favored by certain food elements and inhibited by others. Rettger and Cheplin[9] asserted that certain bacteria may be introduced into the intestine and maintain an existence for a time, retarding the development of other bacteria which are considered harmful. Dragstedt and his co-workers[10] confirmed the observation that diet modifies the flora of the intestine, but stated that if intestinal stasis or acute intestinal obstruction is produced, no matter what the predominating types were before, the putrefactive bacteria promptly become predominant and may be responsible for the intoxication found in those conditions.

One is surprised to find that many of the reports in the literature do not mention that anaerobic cultures have been made; others state that there was no difference between the aerobic and anaerobic cultures. Many authors noted that bacteria frequently were seen in smears which could not be cultivated. Cushing and Livingood,[4] particularly, described a large bacillus which was often present but which would not grow. It is possible that these were anaerobes which could not develop in the degree of anaerobiosis attained by these workers. Others have appreciated the importance of anaerobic cultures.

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5. Libert, Edmond: Le tubage duodenal; Ses applications au diagnostic et au traitement. Considerations sur la flore duodénale normale et pathologique, Paris, 1924.

6. Hoefert, Bruno: Ueber Bacterienbefunde im Duodenalsaft von Gesunden und Kranken, Ztschr. f. klin. Med. **92**:221-225 (Nov.) 1921.

7. Kendall, A. I.: Recent Developments in Intestinal Bacteriology, Am. J. M. Sc. **156**:157-172 (Aug.) 1918.

8. Torrey, J. C.: The Regulation of the Intestinal Flora of Dogs through Diet, J. M. Research **39**:415-447 (Jan.) 1919.

9. Rettger, L. F., and Cheplin, H. A.: A Treatise on the Transformation of the Intestinal Flora, New Haven, Yale University Press, 1921.

10. Dragstedt, L. R.; Cannon, P. R., and Dragstedt, C. A.: Factors Controlling the Intestinal Bacteria. The Effect of Acute Obstruction and Stasis on Bacterial Types, J. Infec. Dis. **31**:209-214 (Sept.) 1922.

With the idea that the anaerobic organisms might be significant in certain types of intestinal obstruction, we have made both aerobic and anaerobic cultures in the present study. We have also attempted to correlate our observations with the anatomic and certain of the physiologic conditions revealed at subsequent operations.

## TECHNIC

In a previous paper, we have described the technic of partial duodenal obstruction in dogs.[2] The principle is to use a living sheet or band of parietal peritoneum and posterior sheath of the rectus from the abdominal wall and to diminish the lumen of the gut to considerable degree without obstructing it completely. All food was withheld from the animals for thirty-six hours before operation, and water was withheld for sixteen hours. Specimens of duodenal fluid were obtained by stripping the gut approximately 10 cm. from the pylorus and clamping 5 cm. of the duodenum thus stripped between two rubber protected clamps. We estimated that this left approximately 0.5 milliliter of fluid, held largely between the crypts and folds of the gut. With a syringe and a no. 16 Luer needle, this segment of the gut was washed thoroughly with 5 milliliters of the supernatant fluid from 0.2 per cent dextrose cooked meat medium from which the air had been driven by boiling. The needle hole was closed with a purse string suture previously laid and tied as the needle was withdrawn. One milliliter of this fluid was then planted into a tube of dextrose cooked meat medium, and 0.1 milliliter was transferred to the first of a series of twelve tubes, each containing 0.9 milliliter of the supernatant broth. After thorough shaking, 0.1 milliliter was transferred from the first to the second tube and so on through the series. Thus each tube contained approximately one tenth of the bacteria present in the preceding tube. Allowing for experimental error, the number of organisms present could be estimated within one digit. The fluid withdrawn after washing the segment of the gut represented an approximate dilution of from 1-10. In the small tubes, the dilutions ranged from one to one hundred to one to ten trillion. The tubes were then incubated under strict anaerobic conditions in a McIntosh and Fildes jar.[11] In this medium under these conditions, both aerobes and anaerobes develop. satisfactorily. After twenty-four hours culture, streaks were made on 5 per cent sheep blood agar plates from the tubes showing growth. One set of plates was incubated aerobically and another set anaerobically. Smears from the broth indicated to what dilution each type of organism had been distributed. On the next day, the plates were examined to confirm the observations in the tubes. Individual colonies could then be fished for further identification. From these tubes and plates, an estimate could be made of the number of viable organisms of each type in the original duodenal fluid. For example, let us say that five of the small tubes showed growth. In the first tube, gram-positive cocci, large gram-positive bacilli and small gram-negative bacilli were found. Gram-positive and gram-negative bacilli were present in the second and third tubes, but only gram-positive bacilli in the fourth and fifth. The anaerobic plates made from the first of these tubes showed the typical large double zoned colonies of *B. welchii*, small gray colonies containing gram-negative bacilli and small colonies of cocci which turned green on exposure to the air. The aerobic plate from the first tube showed only large

11. McIntosh, J., and Fildes, P.: A New Apparatus for the Isolation and Cultivation of Anaerobic Microorganisms, Lancet. **1**:768-770 (April 8) 1916.

gray colonies of gram-negative bacilli and small green colonies of cocci. The anaerobic plates from the second and third tubes developed typical *B. welchii* colonies, and small gray colonies of gram-negative bacilli. The aerobic plates from these tubes showed only large gray colonies of gram-negative bacilli. The anaerobic plates from the fourth and fifth tubes again showed *B. welchii* colonies, while the aerobic plates did not show any growth. From such observations one could estimate that there were between 10 and 100 aerobic gram-positive cocci, between 1,000 and 10,000 aerobic gram-negative bacilli and between 100,000 and 1,000,000 anaerobic gram-positive bacilli in one cubic centimeter of the original fluid.

## EXPERIMENTAL RESULTS

In a preliminary series, the obstruction was made just above the ileocecal valve. In eleven dogs, specimens of fluid were taken from the duodenum, lower jejunum and lower ileum just above the occlusion. The results in this series were unsatisfactory, since all but one dog died as a result of the procedure. The causes of death included general peritonitis, acute obstruction and pneumonia. However, certain of the preliminary results are of interest and are included here, particularly the ante-obstruction observations of bacteria in the duodenum. The results from these eleven normal dogs were added to the figures from the fourteen dogs of a later series in which the obstruction was placed at the lower end of the duodenum. Thus we obtained cultures from the duodenum of twenty-five normal animals.

In the early experiments the organisms found in the lower intestine belonged to many types which could not be classified, and a complete analysis was not practical. However, the bacteria in the duodenal fluid were few in number and variety and in almost all cases could be isolated and identified. It soon became evident that there were three principal bacterial groups, namely, aerobic gram-negative bacilli of the *B. coli* group, aerobic gram-positive cocci of the nonhemolytic or green streptococcus group and anaerobic gram-positive bacilli of the *B. welchii* group. Other organisms rarely found were *B. proteus, Staphylococcus aureus* and *albus, B. sporogenes* and certain gram-positive aerobic bacilli. In the later experiments, no attempt was made to classify the organisms further than to put them into one of these three groups. The results are given in table 1.

A survey of these results brings out certain points of more or less significance. First, let us take the normal series. In only one of the twenty-five (4 per cent) was the duodenum sterile. In seven, the Welch bacilli existed alone. In three, the streptococci and in one the colon bacilli existed alone. In six, all three forms were found. The cocci were present in fourteen and absent in eleven. The gram-negative bacilli were present in eleven and absent in fourteen. The gram-positive anaerobic bacilli were present in seventeen and absent in eight. It is seen that the gram-positive anaerobic bacillus was the type most con-

sistently found in the duodenum of the dogs of our series. If anaerobic cultures had not been made, 32 per cent instead of 4 per cent would have been considered sterile.

One is struck by the high counts in four of this series of normal dogs. We cannot explain this inconsistency except to suggest that in some way or other there was a high intake of bacteria just before operation. There is a possibility that the dogs were fed, although the caretakers deny this, and no food was found in the stomach at operation. It is significant that these animals were all operated on within a single week. It is possible that they were a poorly nourished group. With these exceptions, the bacterial count of the normal duodenum of our dogs was low.

TABLE 1.—*Results of Duodenal Obstruction in Dogs.*

| Number | Laboratory Number | Before | | | Day P.O. | Degree of Obstruction | Second Operation | | | Day P.O. | Degree of Obstruction | Third Operation | | | Day P.O. | Degree of Obstruction | Fourth Operation | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | +C | —B | +B | | | +C | —B | +B | | | +C | —B | +B | | | +C | —B | +B |
| 1 | 8081 | 0 | 1 | 1 | .. | ..... | .. | .. | .. | .. | ..... | .. | .. | .. | .. | ..... | .. | .. | .. |
| 2 | 8097 | 0 | 0 | 1 | .. | ..... | .. | .. | .. | .. | ..... | .. | .. | .. | .. | ..... | .. | .. | .. |
| 3 | 8098 | 0 | 1 | 1 | .. | ..... | .. | .. | .. | .. | ..... | .. | .. | .. | .. | ..... | .. | .. | .. |
| 4 | 8103 | 0 | 0 | 1 | .. | ..... | .. | .. | .. | .. | ..... | .. | .. | .. | .. | ..... | .. | .. | .. |
| 5 | 8104 | 0 | 0 | 1 | .. | ..... | .. | .. | .. | .. | ..... | .. | .. | .. | .. | ..... | .. | .. | .. |
| 6 | 8105 | 4 | 1 | 0 | .. | ..... | .. | .. | .. | .. | ..... | .. | .. | .. | .. | ..... | .. | .. | .. |
| 7 | 8110 | 0 | 0 | 1 | .. | ..... | .. | .. | .. | .. | ..... | .. | .. | .. | .. | ..... | .. | .. | .. |
| 8 | 8126 | 1 | 1 | 1 | .. | ..... | .. | .. | .. | .. | ..... | .. | .. | .. | .. | ..... | .. | .. | .. |
| 9 | 8135 | 1 | 0 | 1 | .. | ..... | .. | .. | .. | .. | ..... | .. | .. | .. | .. | ..... | .. | .. | .. |
| 10 | 8147 | 1 | 0 | 0 | .. | ..... | .. | .. | .. | .. | ..... | .. | .. | .. | .. | ..... | .. | .. | .. |
| 11 | 8150 | 1 | 1 | 0 | .. | ..... | .. | .. | .. | .. | ..... | .. | .. | .. | .. | ..... | .. | .. | .. |
| 12 | 8190 | 2 | 0 | 0 | 17 | + | 0 | 2 | 1 | 81 | ++ | 4 | 4 | 4 | 119 | +++ | 5 | 5 | 4 |
| 13 | 8191 | 3 | 0 | 2 | 17 | ++++ | 5 | 5 | 4 | 77 | ++++ | 4 | 4 | 4 | 121 | ++++ | 1 | 4 | 3 |
| 14 | 8201 | 1 | 0 | 0 | — | — | — | — | — | — | — | — | — | — | — | — | .. | .. | .. |
| 15 | 8202 | 1 | 0 | 0 | — | — | — | — | — | — | — | — | — | — | — | — | .. | .. | .. |
| 16 | 8209 | 1 | 1 | 1 | 10 | + | 1 | 0 | 2 | 70 | ++ | 4 | 4 | 4 | 119 | ++ | 3 | 3 | 1 |
| 17 | 8295 | 0 | 0 | 0 | 39 | ++ | 6 | 3 | 6 | 108 | ++ | 3 | 6 | 4 | .. | ..... | .. | .. | .. |
| 18 | 8313 | 0 | 1 | 0 | 35 | ++ | 3 | 3 | 3 | — | — | — | — | — | .. | ..... | .. | .. | .. |
| 19 | 8314 | 0 | 0 | 2 | 35 | +++ | 0 | 4 | 4 | 80 | +++ | 2 | 3 | 2 | .. | ..... | .. | .. | .. |
| 20 | 8332 | 5 | 3 | 5 | 49 | ++ | 5 | 5 | 0 | 70 | +++ | 5 | 6 | 5 | .. | ..... | .. | .. | .. |
| 21 | 8333 | 0 | 0 | 1 | — | — | — | — | — | — | — | — | — | — | .. | ..... | .. | .. | .. |
| 22 | 8360 | 5 | 7 | 7 | 49 | ++ | 5 | 7 | 6 | 59 | ++++ | 3 | 3 | 6 | .. | ..... | .. | .. | .. |
| 23 | 8361 | 5 | 7 | 7 | 45 | ++ | 6 | 6 | 4 | 80 | +++ | 7 | 7 | 4 | .. | ..... | .. | .. | .. |
| 24 | 8364 | 3 | 5 | 3 | 45 | ++ | 6 | 9 | 7 | 79 | +++ | 2 | 5 | 5 | .. | ..... | .. | .. | .. |
| 25 | 8417 | 0 | 0 | 1 | 30 | ++++ | 5 | 0 | 5 | 63 | ++++ | 0 | 5 | 4 | .. | ..... | .. | .. | .. |
| 26 | 8418 | — | — | — | 32 | + | 0 | 0 | 3 | 66 | ++ | 5 | 6 | 4 | .. | ..... | .. | .. | .. |

In this table and in table 2, 0 indicates no growth; 1, from 1 to 100 per cubic centimeters; 2, from 10 to 100 per cubic centimeter; 3, from 100 to 1,000 per cubic centimeter; 4, from 1,000 to 10,000 per cubic centimeter; 5, from 10,000 to 100,000 per cubic centimeter, etc. + indicates slight dilatation; ++, moderate dilatation; +++, marked dilatation; ++++, extreme dilatation. +C indicates gram-positive cocci; —B, gram-negative bacilli; +B, gram-positive bacilli. Figures in the "Days P.O." column are the number of days after the production of an obstruction was present in the duodenum.

Eleven of these animals and one other which did not have an anteobstruction culture taken, were reexamined after a partial obstruction had existed in degree varying from slight to extensive for from ten to forty-nine days.

In none of the twelve examinations was the gut found sterile. In only one did a single type exist alone, and that was the gram-positive anaerobic bacillus. In six, all three forms were found. The cocci were present in nine and absent in three. The gram-negative bacilli were

present in ten and absent in two. The gram-positive anaerobic bacilli were present in eleven and absent in one. It is seen that there was a striking increase in all types. In general, the greatest increase in numbers was found when the greatest dilatation was present, but this was not invariable. Fluoroscopic examinations as reported in the previous paper revealed the fact that the delay in emptying almost always corresponded closely to the degree of dilatation.

It is seen that certain types were present after obstruction which were not found before, and vice versa; also that the type predominating before had no certainty of predominating afterward. In general, the gram-negative bacilli increased more than the others but not strikingly, as Dragstedt [10] reported for his cases of acute obstruction.

When little obstruction was present, it was increased slightly at the time of the second operation by tightening the band. When eleven of the animals were examined a third time, from fifty-nine to 108 days after obstruction, it was found again that in no case was the duodenum sterile, and in no instance did a single type exist alone. In ten, all three types were present. The cocci were present in ten and absent in one. The gram-negative bacilli and the gram-positive anaerobic bacilli were present in all instances. It is seen also that there was a general increase in the number of all three types. Again, it is seen that the predominating type changed, and that the gram-negative bacilli gained more than the others. In every instance but one, the degree of dilatation either had been maintained or had increased.

Three animals were examined a fourth time, from 119 to 121 days after obstruction, and again the gut was not sterile in any instance. In all of the cases all three types were present, but the numbers were less than at the time of the preceding examination. The gram-negative bacilli, however, maintained their numbers better than either of the others. The degree of dilatation was somewhat increased.

In eleven of the twelve dogs having a third or fourth examination, cultures were made not only of the fluid in the gut above the obstruction but also of that from the lower jejunum for comparison. The gut immediately below the obstruction frequently was found collapsed, and in the region of the middle of the gut this condition was also often present. In seven of these cases the number of organisms in the lower jejunum was less than in the duodenum above the obstruction. In three of these seven, certain types which were present above the obstruction were absent below. These results are shown in table 2.

At the same time, cultures were made of bile taken from the gallbladder by aspiration without primary dilution. In six of the eleven cases, organisms were found in considerable numbers. These observations are of great interest and warrant a more extensive study.

## COMMENT

Certain of our observations corroborate the work of previous observers. Aerobic bacteria were present in the majority of duodenums of our normal dogs for a considerable length of time after the passage of food through the duodenum. With anaerobic organisms also considered, it was found that the duodenum was rarely sterile. The viable bacteria were enormously increased in number after chronic or partial obstruction of the duodenum which produces a delay in the passage of intestinal contents and some degree of distention and hypertrophy of the gut above the obstruction. This relative increase in the viable organisms in the stripped gut was striking, but attention should be called to the fact that the dilated lumen filled with material made the actual increase even greater. The amount of fluid probably did not vary more than three or four times the estimated quantity in any case, while the number of bacteria per milliliter increased thousands of times. This increase is probably caused by a multiplication of the bacteria in

TABLE 2.—*Results of Duodenal Obstruction in Dogs Shown After A Third or Fourth Examination*

| Number | Laboratory Number | Number of Operations | Day of Obstruction | Degree of Obstructions | Above | | | Below | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | +C | −B | +B | +C | −B | +B |
| 1 | 8190 | 4 | 119 | +++ | 5 | 5 | 4 | 5 | 5 | 2 |
| 2 | 8191 | 4 | 121 | ++++ | 1 | 4 | 3 | 5 | 7 | 7 |
| 3 | 8209 | 4 | 119 | ++ | 3 | 3 | 1 | 5 | 5 | 0 |
| 4 | 8295 | 3 | 108 | ++ | 3 | 6 | 4 | 1 | 7 | 7 |
| 5 | 8314 | 3 | 80 | +++ | 2 | 3 | 2 | 1 | 5 | 3 |
| 6 | 8332 | 3 | 70 | +++ | 5 | 6 | 5 | 1 | 5 | 4 |
| 7 | 8360 | 3 | 59 | ++++ | 3 | 3 | 6 | 0 | 0 | 2 |
| 8 | 8361 | 3 | 80 | +++ | 7 | 7 | 4 | 3 | 4 | 3 |
| 9 | 8364 | 3 | 79 | +++ | 2 | 5 | 5 | 2 | 2 | 1 |
| 10 | 8417 | 3 | 63 | ++++ | 0 | 5 | 4 | 0 | 0 | 0 |
| 11 | 8418 | 3 | 66 | ++ | 5 | 6 | 4 | 4 | 7 | 6 |

the duodenum. Any delay of food in the stomach favors a great destruction of bacteria, but when the food mass has passed the pylorus, it comes in contact with the duodenal fluids which have a much weaker antiseptic action.

The great variability of the flora from time to time in animals with duodenal obstruction, with a predominance of now one and now another type, suggests that the bacteria are constantly changing, and that this variation depends on the intake and survival of the different types of bacteria rather than on the variance of the local conditions. But there is some evidence that the conditions tend to favor the predominance of the gram-negative organisms. When bacteria are growing together in large numbers, the question of their interaction becomes an important one. In a number of instances there seemed to be an inhibition of the growth in the test tube of the gram-positive anaerobic bacilli cultured from our animals by the gram-positive aerobic cocci. The symbiosis

and antagonism of bacteria are questions which have been studied greatly but have not been elucidated. Castellani [12] has recently made some simple and convincing experiments which indicate definitely that certain organisms when growing together may perform certain functions which neither could accomplish alone.

The fact that down in the middle of the intestine the viable bacteria were frequently less than above the obstruction suggests that, with the passage of the food mass and a collapse of the tube, there may be some antiseptic action by the gut mucosa on the bacteria in immediate contact with it. It is probable that many bacteria penetrating the wall are destroyed. Radel,[13] tried but failed to demonstrate any growth-inhibiting substance in extracts or emulsions of the stomach or intestinal wall, and suggested that whatever the antiseptic action, it must be a function of living cells. This may be something of the same nature as that which prevents digestion of the living mucosa by the digestive fluids.

Our observations with regard to the presence of bacteria in the bile of certain of the dogs with duodenal obstruction is of considerable importance and will be continued and carefully controlled. A report will be made in a subsequent paper.

It has been found repeatedly by many observers that the lower gut is in contact with billions of organisms, while the duodenum normally is not. The question arises whether the lower gut normally has any resistance to the action or invasion of these organisms which the duodenum has not. May such resistance be developed by the duodenum after prolonged contact with them? Although the cases are too few to draw conclusions, there is a suggestion, in the falling off in numbers of bacteria in the examinations made in the later stages of obstruction, that this feature of the problem may well merit investigation. One is reminded of the intestinal immunity results of Besredka in this connection.[14]

## SUMMARY

1. In the duodenum of our dogs, bacteria were normally present. In 70 per cent of cases anaerobic gram-positive bacilli of the *B. welchii* type were found. In 50 per cent, varieties of the nonhemolytic strepto-

12. Castellani, A.: The Importance of Symbiosis or Close Association of Different Species of Organism in the Production of Certain Biochemical Phenomena and in the Causation of Certain Diseases and Certain Symptoms of Diseases, J. A. M. A. **87**:15-22 (July 3) 1926.

13. Radel, F. W.: Sind in der Dünndarmschleimhut Bakterienwachstüm Hemmende Stoffe (Bakteriostanine) nachweisbar? Ztschr. f. d. ges. exper. Med. **48**:658-670, 1926.

14. Besredka, A.: Immunisation Locale Pansements Spécifiques, Paris, Masson & Cie., 1925.

cocci group and in 40 per cent members of the *B. coli* group were present. Thus the anaerobic gram-positive bacilli were the most consistent but were not invariably present.

2. After partial obstruction of the duodenum, these organisms were found in enormously increased numbers varying with the degree of obstruction and the extent of dilatation of the intestine above the obstruction. The greatest increase in numbers was with the bacilli of the *B. coli* group, but there was no striking difference between this and the other types.

3. This increase was maintained for a considerable period, but in some cases there was a decrease later, even though the obstruction persisted.

4. The flora of the duodenum in any particular animal was not constant, now one and now another type predominating.

5. The gut immediately below the obstruction was usually more or less collapsed. In more than half of the cases of this series, there were fewer viable organisms in the lower jejunum far below the obstruction than in the gut just above the obstruction.

# A REVIEW OF UROLOGIC SURGERY

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## KIDNEY

*Surgical Technic.*—Bugbee [1] cites cases to illustrate problems of renal surgery. These case reports and the discussion of them emphasize the following points:

Hematuria, however slight, may be of extreme importance and should never be passed over without thorough and repeated study. By such means renal tumors will be diagnosed much more often, and in their incipiency, when cure may be possible.

There are many and varied types of renal tuberculosis, the more chronic forms being probably often misunderstood. Nature develops remarkable resistance to this type of infection. Such resistance should be utilized to the fullest in the treatment of these cases.

Anomalous renal vessels as a cause of ureteral obstruction and resulting hydronephrosis are more common than has been believed previously. Pyelography in these cases may give a fairly definite picture. Temporizing is of no avail.

Renal calculi call for a most careful study of each case, the best judgment in outlining the proper procedure to be followed and careful operative technic.

Conservatism in deciding on operation, the proper preparation of the patient for operation, conservation of renal tissue, nephrotomy preliminary to nephrectomy in the presence of serious surgical risk, the free employment of transfusion and intelligent after-care will go far toward placing renal surgery in its proper place as one of the most interesting, accurate and satisfactory branches of surgery.

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1. Bugbee, H. G.: Some Interesting Problems in Renal Surgery, J. Urol. **15**:431-448 (May) 1926.

*Nephritis.*—Damski [2] reports a series of cases of nephritis surgically treated. Kummel has operated in forty-seven similar cases. In twenty-eight he performed unilateral and in five bilateral decapsulation; ten patients died after a period of temporary improvement, twelve were cured, eight improved and three were unchanged. Of those who were cured, two have lived eighteen years, one twelve years, one thirteen years; two have been well five years, and two died from other diseases after ten years of good health. Five of nine patients on whom nephrotomy was performed recovered; two were improved and two died. Rovsing's statistics of his eighty-seven cases together with sixty-nine from other Danish surgeons are as follows:

Of sixty-two patients with interstitial nephritis treated surgically, fifty-three were cured, eight were improved and one died. Of fifty-six patients with parenchymatous nephritis and albuminuria, twenty-four were completely cured, twenty were improved, two remained unchanged and nine died. Of twenty-four patients with nephrosis (unilateral in two), eight were cured, nine were improved, four remained unchanged and three died. Of nine patients with chronic glomerulonephritis four were cured, four were improved, and the condition of one remained unchanged.

Pousson operated in eleven cases of chronic nephritis, complicated by progressive oliguria, anuria and edema. Fourteen operations were performed (bilateral and unilateral decapsulation and nephrotomy). In five cases death occurred during the first seven days after operation; in two, death occurred two years later, and in two, the patient was alive six years after operation. In the cases in which death did not occur at once there was immediate diminution of the edema and amelioration of the general symptoms. Casper has operated in fifty cases. He states that surgical measures ameliorate the symptoms but do not cure the disease.

Damski reports twenty-four cases in which he operated during the last six years. In ten there was complete cure, in seven improvement, and in seven death resulted; two of the latter were cases of mercurial poisoning, and in one case death was due to pulmonary tuberculosis. In four, death was considered due to operation.

*Anomalies.*—Bouchard,[3] after a study of primitive congenital dilatation of the upper portion of the urinary tract, believes that this type of dilatation deserves to be individualized. It constitutes by itself a distinct anatomicoclinical type of congenital anomaly of the urinary tract. It may be unilateral or bilateral, total, involving the pelvis and ureter, or

2. Damski, A.: Sur le traitement chirurgical des néphrites, J. d'urol. méd. et chir. **21**:203-226, 1926.

3. Bouchard, René: La dilatation congenitale primitive des voies urinaires superieures, J. d'urol. méd. et chir. **21**:412-431, 1926.

segmentary, involving only part of the excretory tract. The ureteral orifices may take part in the process. The congenital nature of the lesion is suggested by the extent of the dilatation, the early age at which it usually occurs, the absence of mechanical obstructions or of cerebrospinal lesion, the occasional bilateral incidence of the condition and the association of other well recognized congenital malformations, such as polycystic kidneys, coccygeal anomalies, spina bifida and hypospadias. The author advocates the pathogenic hypothesis that the anomaly affecting the urinary apparatus of the kidney results from a dystrophic condition similar to that causing polycystic kidneys. This dystrophic condition is of the same group as that which brings about megalavesica and megacolon. The congenital lesions seem to affect primarily the nerve fibers, which brings about atony and, later, dilatation of the pelvis and ureters. The slight hypertrophy of the muscular coat, found on histologic examination, explains the fight of these ducts against the dynamic troubles with which they are confronted. Cases of segmentary dilatation are due to limited involvement of the urinary sympathetic plexus. On the other hand, some cases probably result from the persistence of the relative dilatation of the ureter and kidney existing in the fetus till the fifth month. The symptoms are not clear. Many cases, particularly those of the segmentary type, remain latent. Chronic incomplete retention is often the accident which reveals the others. In most cases there is a remarkable adaptation of the organism, with the maintenance of renal secretory activity sufficient to support life, in spite of the extent of the lesion. The diagnosis is impossible without a complete urologic examination. A simple cystoscopic observation is sufficient to make the diagnosis in cases in which the dilatation extends to the ureteral orifices. Ureteral catheterization may sometimes be a guide in showing pelvic retention or in exhibiting a vesicorenal "reflux." Valuable diagnostic help is derived from pyelography and cystopyelography.

Walther [4] reports a case of bilateral double renal pelvis and ureter in a woman, aged 65. Cystoscopy, because of pyuria and pain under the right shoulder blade and in both flanks, showed double ureteral orifices on the right and left; a pyelogram made of each side showed complete duplication of pelvis and ureter on each side. There was infection of the lower part of the pelvis on the left. The patient died and the condition was demonstrated at necropsy.

In commenting on complete bilateral duplication of the pelvis and ureter, Walther states that this case brings the total number reported up to fifty-one. The condition represents from 6 to 27 per cent of the anomalies of the upper part of the urinary tract, according to various investigators. The importance of always looking for a second ureteral

4. Walther, H. W. E.: Bilateral Duplication of Renal Pelves and Ureters, Ann. Surg. 82:968-970 (Dec.) 1925.

ostium on each side as a part of cystoscopic routine is emphasized. The hurried examination of the vesical mucosa and failure to carry out indigo-carmine tests of function in cases of suspected double ostium, as well as the omission of urography, account for the failure to recognize many of the cases. The fault lies with the cystoscopist who overlooks such conditions.

[Ed. Note.—It is a commendable routine to look over the surrounding area of the bladder, the trigon and the sphincteric region for second openings. The value of pyelography in demonstrating this anomaly cannot be stressed too much. If a unilateral pyelogram seems incomplete and the pelvis small in relation to the renal shadow, or if certain calices are apparently missing from the upper or lower pole, the possibility of a second pelvis or ureter should be borne in mind, and further search for a second ureteral orifice should be made. The most common anomaly in the urinary tract is duplication of the renal pelvis and ureter; such duplication may be unilateral or bilateral, complete or incomplete. An excellent review of 300 cases, largely from the literature, is given by Mertz in a recent series of articles. It is of interest that in 27 per cent of these the duplication was bilateral.

The comparatively large number of cases of bilateral duplication which have been reported in the literature may be explained by the fact that this unusual condition is reported, while the more ordinary unilateral condition is not. The comparatively common occurrence of ectopic ending of the duplicated ureter as reported in the literature probably is also exaggerated and can similarly be explained.

The incidence of pathologic complications and surgical lesions is high. The most common lesion requiring surgical treatment is hydronephrosis, caused usually by the obstruction of one ureter. Whether or not this occurs at the point where the ureters cross one another and is the result of this crossing, as suggested by Pawloff, has not been definitely proved. It seems probable, however, that in some cases the ureteral obstruction is the result of stricture due to congenital anatomic defect. In some cases stricture in the lower ureter is associated with marked dilatation of the ureter above, comparatively little dilatation of the renal pelvis itself and marked cicatricial pyelonephritis in the peripelvic renal tissue. In cases of extensive hydronephrosis, the surrounding tissues usually become atrophied, and the infection may spread to the other renal segment.

Chronic tuberculosis confined to one pole of a single kidney, if the lesion is caseated or fibrous and walled off from the remaining apparently normal renal tissue, may easily be confused with tuberculosis which affects one segment of a double kidney. The pelvis of the diseased segment may be obliterated and the ureter be atrophied or involved in

localized perirenal adhesions, and thus difficult to identify. The original pelvic duplication of the kidney has doubtless occasionally been overlooked.]

Eisendrath, Phifer and Culver [5] review the cases of horseshoe kidney reported in the literature and add three of their own. This anomaly occurs about once in from 715 to 862 necropsies. The halves may be symmetrical or asymmetrical. As a rule they lie at an equal distance from the spine, but one or both halves may be displaced, one half lying close to the spine and the other half far away. As a rule, the lower poles converge. The isthmus joins the lower poles in about 90 per cent of the cases, the upper poles in about 10 per cent. In seven of the cases studied, the isthmus was fibrous, but in the majority it was composed of parenchyma without any line of division between the halves. The transition to the so-called cake kidney is mentioned as being present in many cases so that there may be an area of demarcation between the two kidneys. In two cases only was the isthmus found behind the aorta.

In most cases there was a complete pelvis in each half, yet duplication of the pelvis or double pelvis in one side or both was encountered at times. In horseshoe kidney the calices are at times extrarenal and end independently in the ureter. As a rule the ureters pass across the isthmus. Sometimes the isthmus itself may have an independent ureter. Usually calices are present only in the upper half or two-thirds, but an extrarenal calix may drain the isthmus and may be opened during the operation of heminephrectomy.

The site of the horseshoe kidney may be anywhere from the normal level to the true pelvis, although it usually is below the aortic bifurcation. The fixation is in a measure due to the fact that it has multiple blood vessels supplying it, all from immediately adjacent trunks. Multiple vessels for each half and often for the isthmus as well are found in 80 per cent of the cases. The importance of this in operative considerations is obvious.

The course of the ureter across the isthmus, the abnormal site of the pelvis on the ventral aspect of the kidney, the frequent insertion of the ureter at a point higher than the bottom of the pelvis and the frequent absence of a pelvis are productive of pathologic conditions. Congenital stricture of the ureter is common in cases of horseshoe kidneys, and the presence of many anomalous vessels adds to the possibility of ureteral obstruction.

There are no symptoms pathognomonic of the anomaly. Abdominal pains are presumably due to the pressure of the isthmus. The most characteristic feature of these pains is their increase when the patient leans forward or exerts himself, and their complete disappearance when the patient lies down.

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5. Eisendrath, D. N.; Phifer, F. M., and Culver, H. B.: Horseshoe Kidney, Ann. Surg. **82**:735-764 (Nov.) 1925.

The diagnosis of horseshoe kidney may be determined by palpation. Since the advent of urography, diagnosis by palpation is less frequent. Roentgenographic evidence consists of the close proximity of one or both renal shadows to the spine at a lower level than normal, and the close proximity of shadows of renal calculi to the spine, or the obliquity of their position in relation to it. If, however, one or both halves are symmetrical, that is, at the same level and as far away as the normal kidney, the roentgenographic data are of little help. Pyelography is the method that corroborates the suspicions aroused by the roentgen-ray observations. If one or both pyelograms lie in close proximity to the spine at the same or different levels or even extend partly across the spine, there can be little or no doubt of the presence of horseshoe kidney. Braasch called attention to the finding of one or more calices directed mesially, long narrow pelves, and the unusual course of the ureter passing behind the calix and not entering the pelvis along its convex border.

Eisendrath, Phifer and Culver recommend the extraperitoneal route in operating. It is frequently necessary to extend the incision to the outer border of the corresponding rectus muscle because access to the pelvis must be from the ventral and not from the dorsal aspect, as in ordinary pyelotomy. The peritoneum may be displaced while the patient is in the lateral position, and then the patient may be placed in a supine position while the pelvis and isthmus are being explored. For heminephrectomy a good exposure is essential owing to the many accessory vessels that enter the hilum, poles and isthmus in an irregular manner. The isthmus may be clamped as one proceeds to divide it, and the denuded areas closed by mattress sutures of chromic catgut reinforced at loop and knot by fat pads.

[ED. NOTE.—This is an excellent review of the anatomic, pathologic and surgical features of an anomaly that has been much discussed in American and European literature during the last five years. The importance of correct diagnosis, which can usually be made by the proper application of urologic methods, is to be emphasized. The authors contribute little that is really new to our knowledge of the condition, but in a clear way they have epitomized the essential practical features of its pathology.]

*Hydronephrosis.*—Hinman and Hepler,[6] in a comprehensive set of experiments, have undertaken to determine the causal relation between some of the recognized factors in the formation of the urine and hydro-

6. Hinman, Frank, and Hepler, A. B.: Experimental Hydronephrosis: The Effect of Changes in Blood Pressure and Blood Flow on Its Rate of Development: I. Splanchnotomy: Increased Intrarenal Blood Pressure and Flow; Diuresis, Arch. Surg. **11**:578-585 (Oct.) 1925. Hinman, Frank, and Hepler,

*(Footnote continued on following page)*

nephrosis. Some of these factors were experimentally modified over long periods of time, thus increasing (diuresis) or diminishing (oliguria) urine formation; the effect of such changes on the rate of development of hydronephrosis was noted. The effect of more direct alteration of intrarenal pressure and blood flow was studied. To determine the gross changes in the kidneys, stereoscopic roentgenograms were made after intra-arterial injections of barium sulphate; the capacities of the renal pelves were measured, and the kidneys were then sectioned and studied further. The discussion of experimental results has been summarized under the following heads.

*Splanchnotomy.*—Complete obstruction of a ureter in rabbits was followed by the progressive development of hydronephrosis. The degree of hydronephrotic atrophy was proportional to the duration of the obstruction. Unilateral splanchnic neurectomy caused diuresis on the side of operation as the result of vasodilatation, with an increase in the blood flow through the kidney. This diuresis persisted for long periods. Unilateral interruption of the splanchnic supply after complete ligation of the ureter had no influence on the rate of development of the hydronephrosis.

*Partial Obstruction of the Renal Artery.*—In this group of experiments, the renal artery was partially compressed and permanent unilateral oliguria produced by diminishing the blood flow and intrarenal blood pressure. It was noted that: 1. Urinary secretion could be reduced by a properly placed, partially obstructing rubber tube on the renal artery. 2. With the blood flow and the intrarenal blood pressure reduced and the ureter on the same side totally ligated, hydronephrosis developed to a much greater degree and more rapidly than when the ureter alone was ligated. 3. The increase in the rate of development of hydronephrotic atrophy in the presence of reduced secretory pressure and of pressure atrophy are important factors, but the nutritional factor is an equally or more potent one in the production of hydronephrosis. 4. Rapid parenchymal degeneration resulting from anemia by arterial compression weakens resistance and accelerates dilatation, in spite of the diminution in back pressure.

*Partial Constriction of the Renal Vein.*—The effect of diminished blood flow, caused by partial obstruction of the renal vein, but with

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A. B.: Experimental Hydronephrosis: The Effect of Changes in Blood Pressure and in Blood Flow on Its Rate of Development: II. Partial Obstruction of the Renal Artery: Diminished Blood Flow; Diminished Intrarenal Pressure and Oliguria, Arch. Surg. **11**:649-659 (Nov.) 1925. Hinman, Frank, and Hepler, A. B.: Experimental Hydronephrosis: The Effect of Changes in Blood Pressure and in Blood Flow on Its Rate of Development, and the Significance of the Venous Collateral System: III. Partial Obstruction of the Renal Vein Without and With Ligation of All Collateral Veins, Arch. Surg. **11**:917-932 (Dec.) 1925.

increased intrarenal pressure and oliguria, on the rate of development of hydronephrosis is considered in this group of experiments. Partial constriction of the renal vein causes capillary stasis and increase in glomerular pressure. The chief question was whether the latter could so affect secretory pressure as to increase the rate of development of hydronephrosis. Prolonged partial obstruction of the renal vein not only produced diminution of blood flow through the kidney and oliguria, but also increased the intrarenal pressure and, if the degree of obstruction was not too great, increased secretory pressure. When such a procedure was combined with complete ureteral obstruction on the same side, the usual course of development of hydronephrosis was accelerated up to twenty-one days, after which the rate of development followed the type usually seen in the longer periods in simple hydronephrosis. The venous stasis of the early periods was found to be nullified later by the compensatory action of the perirenal collaterals. When the collateral venous system was completely destroyed by ligation, and then partial constriction of the vein combined with complete ureteral obstruction, the rate of development was found to be accelerated for the early periods of hydronephrosis over that even of a simple venous constriction. After twenty-eight days marked shrinkage or secondary atrophy occurred, owing to the marked venous occlusion as a result of failure of a collateral system. The action of the venous collateral system, therefore, was compensatory, and its development or nondevelopment was not an essential factor in simple hydronephrosis. Its failure may therefore be an important one in the rare instances of late secondary atrophy with venous constriction. The initial acceleration in the rate of development of hydronephrosis that occurred with venous constriction was primarily the result of increased secretory pressure, and only secondarily the result of the nutritional disturbance.

*Tuberculosis.*—Westerborn[7] reports the cases of renal tuberculosis treated at the Upsala University Clinic in Sweden from 1901 to 1923. In all there were 151 patients; 100 were males and fifty-one females; 126 were less than 40 years of age. In 121, nephrectomy was performed; in sixty-five, the right and in fifty-six, the left kidney was removed. Complete data were obtainable in 111 of these 121; sixty-six of the patients are living, and forty-five are dead. Two died from intercurrent disease; the remainder died from renal tuberculosis or renal disease. Six died the first month, six from two to six months, and five from six to twelve months after operation; four lived more than ten years. Of the six patients who died the first month after operation two died from pneu-

7. Westerborn, Anders: Das Resultat der Behandlung der Nierentuberkulose in der chirurgischen Universitätsklinik zu Upsala, insbesondere mit Rücksicht auf die Entstehung von Miliartuberkulose nach Cystoskopie und Sondierung, Arch. f. klin. Chir. **139**:699-728. 1926.

monia, one each from uremia, tuberculous meningitis, miliary abdominal tuberculosis, and general peritonitis. In seven (5.8 per cent) of the 121 cases death was considered due to operation. Krönlein reports 5.6 per cent, Zuckerkandl 7.7 per cent, and Wildbolz 2.8 per cent mortality in their series of operative cases. Thirty-six of Westerborn's patients died later from tuberculosis or other renal disease, a mortality of 33.6 per cent; the total mortality (forty-three deaths in 114 cases) was 37.8 per cent. The following were the causes of death: renal tuberculosis in sixteen cases; pulmonary tuberculosis in nine; multiple foci in two; miliary tuberculosis, tuberculous meningitis in four; renal disease in five; operation in seven, and intercurrent disease in two.

Only forty-seven of the 111 patients for whom complete data were obtainable are living and without symptoms of renal tuberculosis. Males are more likely than females to have trouble after operation. This may possibly be due to the frequency of genital infections in men, although from the mortality results associated genital infection apparently produces increased immunity to the infection. Forty-four per cent of patients with associated genital tuberculosis got well; in contrast only 35 per cent of patients without such genital infection recovered. Forty per cent of the men and 73.2 per cent of the women are completely cured; 13 per cent of the men are still having trouble, while all the women living are free from trouble; 47 per cent of the men and 26.8 per cent of the women died. Bilateral tuberculosis occurred in thirteen of the entire number of cases.

[Ed. Note.—In the large series of cases reported from ten to twenty years ago, the operative mortality following nephrectomy was high. Von Schmieden reported a mortality of 25.4 per cent. In 106 cases in which operation was performed between 1890 and 1900, Küster (1902) found a total mortality rate of 18.8 per cent in 297 compiled cases. In recent large series of cases, the percentages are much lower: Boeckel reports 5.8 per cent, and Legueu and Chevassu 5.9 per cent. Israel, in a review of 1,023 cases of nephrectomy, found an operative mortality of 12.9 per cent, and a late mortality rate of from 10 to 15 per cent. Wildbolz asserts that the larger general reviews are not of so much value as the more carefully compiled statistics of individual surgeons. From the reports from several large urologic centers, he reviewed 1,450 cases in which the mortality rate was 5 per cent. Only eleven (2.4 per cent) of 445 of Wildbolz' own patients died following operations. Most of the deaths were due to cardiac or pulmonary complications. Sixty-two per cent of 317 patients operated on at least one year before were cured; 30 per cent were dead, and 8 per cent still had evidence of disease. Fifty-five per cent of 104 patients operated on at least ten years before were completely cured; forty-four died from tuberculosis, mainly of the genito-urinary tract. In Kummell's 188

cases, there was a mortality rate of 7 per cent; of the remaining patients, sixteen died the first year, and fourteen in the next four years. Thirty-nine patients were well from fifteen to twenty years after operation, and thirty-eight from ten to fifteen years.

Twenty-three (2.7 per cent) of 845 patients subjected to nephrectomy for renal tuberculosis at the Mayo Clinic died during the first month after operation. In the earlier cases uremia was the most common cause of death and accounted for the large operative mortality. With the present accuracy of preoperative diagnosis, uremia only rarely causes death. When death occurs following operation from uremia, it is usually due to nontuberculous infection of the opposite kidney, or to chronic nephritis. The common causes of early death after the removal of tuberculous kidneys are peritonitis and pulmonary complications, such as empyema, pneumonia and pulmonary embolism.

Israel believes that the chief causes of late postoperative death are pulmonary tuberculosis and tuberculous infection of the opposite kidney. He found, in a series of cases, that more than one-half of all late deaths occurred within two years after nephrectomy. Pulmonary tuberculosis was the cause of death in 45 per cent, tuberculosis of the kidney in 35.9 per cent, and acute miliary tuberculosis in 14 per cent. He also believes that pulmonary tuberculosis existed before operation in 73 per cent of the cases in which it caused death. Meningitis is often the cause of late death. Simmonds found at necropsy that 30 per cent of men with genito-urinary tuberculosis had died from meningitis, only 5 per cent from pulmonary tuberculosis, and none from infection of the genito-urinary tract.]

Darget [8] reported the following case, which has been the source of a long discussion at the Société française d'urologie. A man, aged 51, who had had renal tuberculosis for the last six years, was examined on account of increased frequency and pyuria. The right kidney was enlarged and painful; the left could not be palpated. The "constante d'Ambard" was 0.1, the blood urea 0.35 Gm. and the urine urea 16.2 Gm. Numerous attempts to catheterize the ureters were made, with all possible artifices (epidural anesthesia with morphine; constant irrigation and spinal anesthesia) but none was successful. The capacity of the bladder would not exceed 25 to 30 cc., and the ureteral orifices could not be found. Renal function being good, cystostomy was performed in order to catheterize the ureters, but this also was unsuccessful. Suprapubic drainage was maintained, and the healthy left kidney was explored operatively before excision of the right. Cure followed, although the closure of the cystostomy opening was difficult. Darget

8. Darget, R.: Tuberculose renale ancienne: Impossibilite de catheterisme ureteral par voie cystoscopique et a vessie ouverte: Nephrectomie sur la constante apres lombotomie exploratrice, J. d'urol. méd. et chir. **21**:367-374, 1926.

concludes that catheterization through an opened bladder should not be attempted on account of its uselessness in cases in which cystoscopic ureteral catheterization is unsuccessful. A good "constante d'Ambard" associated with satisfactory exploration of the presumed healthy kidney will be a safeguard against excision of the diseased organ. Michon suggested the use of MacCarthy's urethroscope with injection of indigo-carmin in order to detect the ureteral orifices when cystoscopic catheterization is impossible. If the ureteral catheter is stopped shortly after it enters the ureters, he advises catheterization through a cystostomy opening; this should be successful if one takes care to lift up the inter-ureteral muscle with forceps. Marion favors catheterization through the open bladder, stating that the cystostomy and drainage at least gives relief to the patient. Pasteau also states that when cystoscopic catheterization is impossible, catheterization through an open bladder is easily performed and should always be done. Legueu agrees with Darget and states that one may be unsuccessful in attempting to catheterize through an open bladder. Nephrectomy in those cases may be performed after exploration of the healthy kidney. He cites his statistics of 1,209 cases of renal tuberculosis. In 1,053 in which operation was performed after catheterization, the mortality rate was 1.9 per cent; in 341 cases in which operation was not preceded by catheterization, the mortality rate was 3.9 per cent. Pasteau and Marion do not believe in the safety of nephrectomy performed without preliminary catheterization and only based on the "constante d'Ambard."

[Ed. Note.—When tuberculous infection of the kidney has advanced to such a degree that it is impossible to determine the side of the primary lesion definitely by cystoscopic procedures, it is probable that bilateral infection is present. In some cases it is extremely difficult to rule out the possibility of bilateral infection; one kidney may obviously be diseased while the opposite kidney reveals little evidence of infection. In a series of twenty-two cases at the Mayo Clinic of apparently unilateral tuberculosis, guinea-pigs were inoculated with urine from the supposedly healthy kidney. The results were positive for tuberculosis in seven, and negative in fifteen. In every case two or more guinea-pigs were injected, so that the results may be regarded as fairly accurate. Even with infection in both kidneys, the condition of the bladder may not be any different from its condition in ordinary areal cystitis, and bilateral tests often show that renal function is normal and equal. Pyelography may demonstrate a moderate degree of inflammatory dilatation like that observed with chronic pyelonephritis. Often, however, evidence of cortical necrosis confined to one or more calices will reveal the tuberculous origin. In some of these cases cultures made from the urine from the kidney may show the presence of colon bacilli, which is particularly misleading since the bacteria of secondary infection are not

often found in the cultures from a tuberculous kidney. Microscopic examinations and inoculation of guinea-pigs with the urine obtained from either kidney may be negative. However, if repeated attempts are made to stain the catheterized urine, an occasional acid-fast bacillus may be demonstrated, although this may necessitate the examination of many slides.

Deformity of the bladder and the pathologic changes in the mucosa in cases of renal tuberculosis frequently make the cystoscopic technic more difficult than with any other lesions of the urinary tract. In spite of the progressive improvement in our cystoscopic technic, the great aid offered by sacral anesthesia, and the use of indigocarmin and cystography, cystoscopic technic occasionally fails to identify or locate the disease. A common source of error is an inflammatory proliferation of the mucosa, or granuloma, which may be so extensive as to simulate epithelioma closely. It is not unusual to observe a patient with a persisting suprapubic sinus, after suprapubic cystostomy performed on the assumption that extensive carcinoma of the bladder was present. The proliferation is usually around the infected ureteral orifice, although in many instances it extends across the trigon and may invade other portions of the bladder. It often resembles epithelioma so closely in its papillomatous nature and tendency to bleed that the confusion might be justified.]

Condamin [9] studied a series of 172 cases of renal tuberculosis in which there was no extrarenal lesion. Nephrectomy resulted in cure in 69 per cent; the operative mortality was 2.9 per cent, and the late mortality was 27.5 per cent. In contrast to this, in a group of fifty-three cases of both renal and extrarenal tuberculosis, nephrectomy resulted in cure in only 47 per cent. Nine per cent of patients with coexisting pulmonary tuberculosis died following operation, and only 29 per cent recovered completely. Bone lesions have the least effect on the ultimate results: in 62 per cent of eighteen cases complicated by bone lesions complete recovery occurred. In 59 per cent of twelve cases with genital lesions, recovery took place.

Ekehorn [10] investigated the relationship between age and sex and mortality in 1,577 surgical cases of renal tuberculosis. Complete data were obtained in 1,571 cases: 876 patients (57 per cent) were males, and 675 (43 per cent) females. Sixty-four patients were 15 years of age or less. The greatest number of patients, 1,385 (88 per cent), were

9. Condamin: Des tares apportées aux résultats de la néphrectomie pour tuberculose uniláterale par des localisations tuberculeuses extra-rénales, J. d'urol. méd. et chir. **21**:31-38, 1926.

10. Ekehorn, Gustav: Ueber die Frequenz der Nierentuberkulose im Verhältnis zum Alter und Geschlecht der Patienten, Deutsch. med. Wchnschr. **1**:615-616, 1926.

from 16 to 50 years of age. About one-sixth of the general population, that is, about 17 per cent, are more than 51 years old. In his series 122 (7.8 per cent) were between the ages of 51 and 75, and of this number four were between 71 and 75.

Blatt [11] reports a series of cases of open cavernous tuberculosis. This type of case is often seen, and it is the opposite of the occluded condition as described by Zuckerkandl and Braasch. Wolff reported eighty-eight cases of occluded renal tuberculosis, the distinguishing feature of which is complete isolation of the kidney from the bladder by stricture of the ureter. Blatt found five cases of open, cavernous, renal tuberculosis without vesical symptoms in a series of 130 cases treated operatively. He believes that this type of lesion, the bladder not being involved, is caused by an unusual strain of the bacilli of tuberculosis that affects the kidney alone.

Perret [12] describes his technic of nephrectomy. His experience with a series of cases without a death included eighty-seven in which nephrectomy was performed for tuberculosis. Perret does not use the oblique incision, but the high transverse lumbar. He believes, with Bazy, that the incision must first of all facilitate the most dangerous and important step of the operation. In cases of nephrectomy, this step is represented by the freeing of the superior pole and the preparation, ligature and cutting of the vascular pedicle; the ureter is not severed as is often thought. The incision is extended up to the lateral border of the quadratus lumborum; a tube should be placed there to drain the inferior culdesac of the renal pouch. If after complete cicatrization of the wound, a secondary abscess forms around the ureter, it will penetrate through the muscle layers. During the "décollement," or liberation, the kidney should be left in place without handling, as most of the immediate complications of nephrectomy, such as tuberculous meningitis, miliary dissemination, reflex anuria, embolism and infection of the wound, are caused by unnecessary maneuvers which traumatize the kidney and cause traction on its pedicle. Perret does not attempt to remove a large section of the ureter. He removes only 5 or 6 cm., believing that, if an abscess does form around the severed stump of the ureter, it had better be high in the wound, in a drained area, rather than low, in the pelvis.

Perret does not drain with rubber drains and gauze, as the latter becomes adherent to muscle and peritoneum, functions poorly and is painful to the patient. For more than fifteen years he has used a glass drain, which is replaced by thinner ones on the fifth and tenth days. In this way a firm canal of fibrous tissue forms, through which a sec-

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11. Blatt, Paul: Offene kavernöse Nierentuberkulosen ohne Blasensymptome, Arch. f. klin. Chir. **140**:654-662 (May) 1926.

12. Perret, C. A.: Contribution a la technique de la nephrectomie (en particulier pour tuberculose renal), J. d'urol. méd. et chir. **21**:397-412, 1926.

ondary abscess may eventually find its way to the exterior. In the past, Perret has catheterized the bladder at the end of the operation; sometimes considerable pus, which has probably come down during the operation, is found in the bladder. If the patient awakes and coughs or vomits, this pus may be forced back into the diseased ureter, and may remove the ligature and infect the wound. The bladder is emptied, washed with warm solution of sodium chloride, and injected with from 15 to 20 cc. of a proprietary form of oil of cajuput.

Joly [13] discusses the question of spontaneous cure of renal tuberculosis and cure by medical means. The question can be concisely summarized. Should the patient be advised to submit to nephrectomy as soon as unilateral renal tuberculosis is diagnosed, or are we justified in trying medicinal treatment first, and only advising nephrectomy if these methods fail? The answer depends on the efficiency of medical methods, and on the dangers incurred by delay. Urologists have answered this question definitely. They are unanimous in advising early operation. In considering the duration of the disease, Joly concludes that the disease is rapidly fatal and destroys life much more rapidly than is usually supposed. Statistics are quoted in support of this conclusion. Rafin found that ninety-one out of 168 patients not operated on were dead, the majority within the first three years after the onset of symptoms. Further, only four of these were found to have died from intercurrent disease. In all, about 90 per cent of patients with renal tuberculosis who are not operated on die from their disease. It is noted that the disease is more chronic in females; this is shown in the duration of the disease, in those dying from it, and in those surviving. This probably is due to the tendency of the disease to involve the genital organs in the male.

In answer to the questions: "What is the condition of the survivors?" "Are they cured?" Joly says,

> There is no doubt as to the answer. It is decidedly in the negative. The great majority of the survivors are still suffering from the distressing symptoms of urinary tuberculosis, and in fact, most of them are dying from it. The clinical cures are so rare that they require special mention. They are even so rare that they do not appreciably influence the statistics. We must therefore either look for them in pathological records, or else examine the few isolated cases which have been described as natural cures.

In a careful review of pathologic material, Joly fails to find evidence of actual cure. Cessation of symptoms is more often due to occlusion of the ureter on the affected side or more rarely occlusion of one calix or a portion of the kidney which is tuberculous. In discussing surgical treatment, he finds that 58.9 per cent of his patients are cured, which he notes is strikingly similar to the observations of Judd and Scholl at

13. Joly, J. S.: The Late Results of Renal Tuberculosis, Brit. J. Tuberc. 19:188-195 (Oct.) 1926.

the Mayo Clinic, who quote 58.9 per cent of cures on an average of four years after operation. Further, in tracing the records of the patients who had died, he found a large percentage had died from disease other than tuberculosis.

At present many patients are seen by the urologic surgeon only after the disease is bilateral or advanced. Joly believes that if a diagnosis were made within one year of the first symptoms, the operative mortality would be negligible, the late mortality not more than 10 per cent, and that cure would be ultimately brought about in at least 75 per cent.

[ED. NOTE.—Israel asserts that there is no nonoperative cure for renal tuberculosis, and Wildbolz that it is a disease that is rarely healed spontaneously. It is questionable whether healing ever takes place without operation. On the other hand, in rare cases relatively good health may be enjoyed for many years, even if the infection is extensive. Wildbolz reported cases in which patients with renal tuberculosis lived without marked discomfort for from ten to thirty years. The infection may be well localized and of low virulence, or the patient may, by reason of chronicity and numerous foci of infection, have acquired a tolerance and resistance to the bacillus. Braasch believes that immunity develops with multiplicity of lesions. With removal of the renal focus, complete recovery may take place. In most cases the infection destroys the kidney, spreads locally, extends to the bladder, and often causes disease of the other kidney. Primary nephrectomy is the operation of choice. Conservative surgical procedures are not practical in cases of tuberculous kidneys, and at best afford only temporary relief. Pousson compiled sixty-three cases of nephrotomy for tuberculosis; thirty-nine (61.7 per cent) of the patients died. Von Schmeiden reported seven cases of partial resection; in three the wound healed; in one it healed with a fistula; in two, secondary nephrectomy was necessary; one patient died. Partial resection for tuberculosis is generally a failure, even in cases of double kidney, owing to the fact that an apparently normal renal segment usually is well studded with tubercles. Minute areas of infection may be found readily on histologic examination. Surgical trauma may light up a quiescent area of infection and necessitate further operation later. Good results are usually obtained following nephrectomy. In 358 (58.6 per cent) of 611 cases in the Mayo Clinic in which complete data were obtainable after nephrectomy, cure had occurred on an average of four years after operation; 191 patients (31.2 per cent) were dead. In sixty-two cases (10.1 per cent) there is still evidence of tuberculosis of the genito-urinary tract.]

*Tumors.*—Arkin [14] reports a case of calcification in a hypernephroma of the left kidney producing gastric symptoms. It is of special interest

14. Arkin, Aaron: Calcified Hypernephroma of the Kidney: Report of a Case Diagnosed by X-Ray Examination: With a Discussion of the Differential Diagnosis of Renal Shadows, Surg., Gynec., and Obst. **43**:155-168, 1926.

because of its long duration, sixteen years, and the striking roentgenologic evidence. The tumor was found on fluoroscopic examination of the stomach, which presented an hour-glass deformity. Removal of the calcified hypernephroma by nephrectomy was followed by recurrence in the site of the tumor. The roentgenograms of the tumor taken before operation, and one of the tumor after extirpation of the kidney, present the following conditions: Surrounding the entire shadow of the tumor was a distinctly calcified shell, varying in thickness from 1 to 4 mm. This shell consisted of linear and punctiform shadows, interrupted from place to place by areas of the capsule which contained little calcium. Throughout the entire tumor were distinct and indistinct irregular small shadows of calcification, which assumed a definite arrangement in many parts of the mass. The shadows formed round or oval areas containing less distinct spots and small irregular deposits of calcium. These gave the tumor a lobulated appearance, forming a network of calcified masses separating small and large clearer spaces.

The kidney was 16 cm. in length, nodular and in some areas, hard. It could not be cut with a knife because of calcification, and was cut with a saw. The whole tumor was elliptical in shape and surrounded by a thick capsule of connective tissue containing calcium deposits, and in several places also bone tissue.

Stricker [15] reviews the work done on papillary tumors of the renal pelvis. In 53 per cent of 175 compiled cases, the process was limited to the kidney; in 47 per cent, the process had extended to the ureter or bladder or both. The kidney and ureter alone were involved in thirty-one cases (18 per cent); the kidney and bladder in nine (5 per cent), and all three organs in forty-two (24 per cent). Stricker follows the dictum laid down by Israel in 1901, that in all cases of tumor of the renal pelvis complete nephro-ureterectomy should be performed.

[ED. NOTE.—In a number of the first cases of papillary tumor of the renal pelvis, it was thought sufficient merely to remove the kidney. Later it was noticed that recurrence occasionally developed in the ureter or bladder. If the case has not progressed too far, removal of the kidney and ureter usually will give a good result. The bladder should be examined from time to time to make sure that it does not become involved. In all apparently primary papillomas of the bladder, it is advisable to consider the possibility of an extension from a tumor of the renal pelvis. Clinically, all tumors of the renal pelvis are malignant and readily extend to the ureter and bladder. It is impossible to determine after an examination of the initial lesion what the outcome will be. A number of reported cases of apparently benign primary lesions were quickly followed by malignant extensions or recurrences shortly after operation.

15. Stricker, Oskar: Ueber papillomatöse Geschwülste des Nierenbeckens, Arch. f. klin. Chir. **140**:663-700 (May) 1926.

In both the renal pelvis and the ureter, the individual papillomatous fronds are shorter and broader than similar growths in the bladder; there is more extensive fusion of adjacent fronds, and atypical cell masses are more often seen. Histologically, the growth in the ureter and pelvis contains more areas undergoing malignant degeneration than the comparatively more villous transplants in the bladder, and loss of cellular polarity and regularity, with the presence of numerous mitotic figures, may occur in a grossly benign tumor, as in papilloma of the bladder. In certain cases, the histologic difference in the tumors in the bladder, ureter and renal pelvis is only slight. Lower reported a case in which sections from the kidney, ureter and bladder were histologically similar.

The majority of papillary tumors of the renal pelvis are histologically similar to the malignant papillomas, or the papillary epitheliomas occurring in the urinary bladder. In an occasional case glandular changes have been noted in cells of the papillary structure. If a careful histologic study is made of sections from various parts of tumors of the renal pelvis, small circumscribed areas of malignancy will almost invariably be found, even in the small pedunculated grossly benign papillomas.]

*Leukoplakia.*—Karo [16] reported a case of leukoplakia of the kidney, pelvis and ureter before the Berliner Urologische Gesellschaft. He stated that the case was of eight years' duration and that the leukoplakia formation was on the basis of an infection by the colon bacillus.

[ED. NOTE.—Leukoplakia has long been a subject of interest and conjecture because of its unknown etiology and pathologic significance. The occurrence of such a process in the urinary tract, reproducing exactly the microscopic and gross appearance of skin, together with its relative rarity, have stimulated its study constantly. The urinary tract is derived from entoderm and mesoderm, whereas leukoplakia is an epithelial process. Hinman, Kutzmann and Gibson,[17] in a study several years ago, concluded that leukoplakia played a definite rôle in the development of squamous-cell carcinoma of the urinary tract. A review of the existing theories suggested that leukoplakia was possibly a true metaplasia on the basis of chronic inflammation and irritation, or the biologic process of adaptation to environment in the form of protective cornification. It was also thought that leukoplakia of the urinary tract might arise on the basis of misplaced embryonal rests of primitive ectoderm.

Clinically, the symptoms are those of infection of the urinary tract, urinary lithiasis or conditions with which they may be associated. It

16. Karo, W.: Leukoplakie des Nierenbeckens und Ureters, Ztschr. f. Urol. **20**:208-211, 1926.

17. Hinman, Frank; Kutzmann, A. A., and Gibson, T. E.: Leukoplakia of the Kidney Pelvis, Surg., Gynec., and Obst. **39**:472-489 (Oct.) 1924.

is almost impossible to diagnose except when cystoscopic examination reveals leukoplakia on the wall of the bladder.

Von Borza [18] states that leukoplakia of the urinary tract is relatively rare. It is usually difficult for the cystoscopist to recognize it in the bladder, while in the kidney it can be diagnosed only at operation or necropsy. Numerous theories are cited, most of which favor metaplasia. The author found only three cases in his clinic in a period of years; two of the cases were diagnosed preoperatively and one at operation. One case occurred in a ureteral stump, nephrectomy having been performed for stone sixteen years previously. In the other two cases the leukoplakia was in the renal pelvis; in one there was a squamous-cell carcinoma of the renal pelvis, and in the other a squamous-cell carcinoma of the bladder. For this reason von Borza believes there is a relationship between leukoplakia and carcinoma. In discussing the histogenesis of leukoplakia, von Borza considers that there is more than merely a local irritative factor; it may be based partially on an embryonic basis and partially on an endocrine basis, hormones being brought forth which influence all growth and changes.

Briggs and Maxwell [19] review eighty cases of leukoplakia of the urinary tract. Forty cases were vesical, twenty-four renal, ten ureterorenal, four ureterovesical, and two renal or ureteral or both. They state that the etiology is not understood and no theory has been proposed that explains the majority of cases; even if always associated with stone or specific infection, the genesis of leukoplakia, which histologically is a metaplasia of tissue, would still not be entirely susceptible of explanation. In summarizing, they state that the renal pelvis is probably oftener affected than the bladder; that it may occur at any age and that it is a chronic condition. There are really no pathognomonic signs, but the passage of leukoplakic membrane must be watched for. Leukoplakia of the bladder does not respond to irrigations or instillations and resection; electrodesiccation, radium and nephrectomy must be relied on.

*Cysts.*—Rovsing [20] states that nephrectomy for polycystic kidney is attended by a high mortality. Milkaniewskis in 127 cases of nephrectomy reports a mortality rate of 30 per cent. Death was frequently due to such complications as tuberculosis, calculous pyonephrosis or malignant disease. Rovsing advises exposing the kidneys and puncturing the

18. Von Borza, Jeno: Ueber die Leukoplakie in den Harnwegen mit Bemerkungen über die Ätiologie des Krebses, Ztschr. f. urol. Chir. **19**:194-200, 1926.

19. Briggs, W. T., and Maxwell, E. S.: Leukoplakia of the Urinary Tract with Reports of One Vesical and Two Renal Cases, J. Urol. **16**:1-22 (July) 1926.

20. Rovsing, Thorkild: Die Behandlung der multilokulären Nierenzysten nebst Bemerkungen über die Art Dieses Leidens, Deutsch. med. Wchnschr. **1**:614-615 (April 9) 1926.

individual cysts, thus permitting the kidney to return, at least partially, to its normal size. The cysts usually do not contain urine, and permanent fistulas do not form.

Begg,[21] after a brief review of the literature on the subject of hemorrhagic cysts of the kidney, adopts the description of Brin, who reports twelve cases. This description is as follows:

> The cysts are solitary, and their size as a rule is large. Their extirpation is difficult on account of adhesions to the surrounding organs. The cyst wall is whitish, and the contents consist of red or blackish fluid with old brownish clots. The latter may be black in color, or they may be of white fibrin. The cavity of the cyst is received into the rest of the kidney substance as an egg into an egg-cup. Its wall is continuous with the outer surface of the kidney, without any obvious ridge of demarcation. The internal surface of the cyst wall is irregular and festooned with clots, of which the most superficial are of a dark red or blackish color, and the deepest, grey-white, formed of fibrin, and intimately adherent to the fibrous lining of the cyst. The wall is always much thicker than in the case of the simple serous cysts, and may reach 5 mm. or even 1 cm. in width.
>
> Microscopically, three layers can be distinguished: (1) an inner layer of clots and fibrin; (2) a middle fibrous layer, and (3) an outer layer formed by renal parenchyma atrophied and sclerosed.
>
> Both the part of the kidney containing the cyst and the rest of the organ are clothed in a fibrous capsule of normal thickness. There is rarely a communication with the kidney pelvis.

These cysts are not ordinary serous cysts into which hemorrhage has occurred. Large solitary hemorrhagic cysts are rare. They have few characteristics in common wtih solitary simple cysts and should be placed in a separate category. They are different in nature from blood cysts caused by the degeneration of malignant tumors, from hematonephrosis and from traumatic pararenal cysts. The suggestion is made that these cysts are of the nature of localized hematonephrosis, in which the source of the bleeding remains active for a long time. This source may be in the papillae of the affected portion of the pelvis, and in the case reported an angioma was demonstrated. In some instances the cyst may owe its origin to an angioma in the substance of the kidney itself.

The diagnosis is obscure, and the treatment is total nephrectomy.

*Lithiasis.*—Hinman and Gibson[22] report a case of recurring urinary lithiasis in a physician. Left nephrectomy had been performed because of calculous pyonephrosis, and several operations had been performed on the right kidney because of rapidly recurring stones. This kidney, because of the repeated attacks of stones and infection, was practically destroyed, leaving what appeared to be less functioning renal tissue than is necessary to maintain life. Death was due to cardiac failure and not to uremia. The important points of the case were the rapidity of recur-

21. Begg, R. C.: Solitary Hemorrhagic Cysts of the Kidney: With Report of a Case Originating in a Cavernous Hemangioma, Brit. J. Surg. **13**:649-655 (April) 1926.

rence of the stones after repeated removal, frequent attacks of anuria with high retention of blood nitrogen, the extensive destruction of renal tissue without corresponding functional impairment, and the patient's ability to carry on active practice as a physician in spite of almost total absence of functioning renal tissue. Microscopic examination of the right kidney obtained at necropsy showed extensive parenchymal destruction with replacement by fibrosis and other inflammatory elements; practically no functioning renal tissue could be seen.

*Hematuria.*—Gottlieb [23] reviews the various theories of so-called essential hematuria. Senator advanced the hypothesis of isolated renal hemophilia to explain the process. Israel found in his cases nodes of interstitial nephritis. Klemperer found the condition associated in one of his cases with hysteria and neurasthenia, and advanced the hypothesis that angioneurosis, whereby the blood vessels became widened, allowing diapedesis of the red cells, was the cause of the disease. Golling, in 1909, described nephrosis in thirty-five of forty-seven cases. Wessel, in 1923, described forty-three surgically treated cases. In thirty-four of these he could demonstrate organic conditions such as paranephritic changes, varicose widening of a renal papilla, small aneurysms in the cortex, pyelitis and papilloma of the renal pelvis. In nine cases no pathologic change was found.

Congenital vascular anomalies, nodose glomerulonephritis (Kretschmer) and what Scheele and Klose call "bleeding from a node" are other explanations of the disease.

Two cases are reported by Gottlieb, one in which the kidney removed at operation showed an increase of the connective tissue around the papillae with metachromasia of the cellular elements and widening of the associated collecting tubules. A diagnosis of papillitis renis fibrosa was made. The other case showed no urologic anomaly or pathologic change on close investigation, except the presence of erythrocytes in abundance in the urine. Blood clots were never found. The diagnosis of essential hematuria was made by exclusion. The patient remained unimproved by treatment. Gottlieb considered the bleeding to come from a small node without demonstrable pathologic cause. After a month, 2 per cent silver nitrate solution was instilled into the renal pelvis. This caused some reaction accompanied for four days by increased bleeding and then cessation of hematuria.

In discussing the treatment, Gottlieb expresses the opinion that conservative treatment with instillations of silver nitrate is suited to the

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22. Hinman, Frank; and Gibson, T. E.: Report of a Remarkable Case of Recurrent Urinary Lithiasis in a Physician in Active Practice, with an Unbelievably Small Amount of Renal Tissue; Death, Not from Uremia, but Due to Cardiac Failure, J. Urol. **16**:43-58 (July) 1926.

23. Gottlieb, J.: Ueber die sogenannte essentielle Hämaturia, Ztschr. f. urol. Chir. **18**:237-247, 1925.

cases of papillitis or pyelitis granularis. When there is marked glomerulonephritis, decapsulation is of value. When the bleeding is massive and threatening to life, nephrectomy, or possibly decapsulation, is the procedure of choice. Nephrotomy is discouraged.

Gottlieb feels that the term "bleeding from a node or focus" is a better one than "essential hematuria."

[Ed. Note.—Essential hematuria still remains a discouraging field for study in urology. Certainly, the pathologic changes found are not consistent nor are they clinically or anatomically demonstrable beyond a doubt. Gottlieb's study, while thorough and interesting, adds little that is really new or tangible. It is probable that for some time to come we shall await new evidence concerning the causes of this obscure disease.]

*Renal Function.*—Hélouin [24] says that most urologists have abandoned the intramuscular phenolsulphonphthalein test and use only the intravenous method. He used the latter more than a hundred times without accidents or trouble. The duration of the test is sixty minutes; 3 mg. of phenolsulphonphthalein is diluted with 4 cc. of sodium chloride solution and injected into a vein. The urine is first collected after thirty minutes and again thirty minutes later. The average elimination in normal cases has been: after thirty minutes, from 50 to 60 per cent; during the next thirty minutes, from 18 to 25 per cent, and during the whole hour, from 65 to 85 per cent. Hélouin's work on phenolsulphonphthalein concerns principally its relative value to the "constante d'Ambard" or "K." He concludes that the intravenous phenolsulphonphthalein test and "K" usually give similar results, but from a quantitative point of view one observes differences fairly often which should not be neglected. In general, the test which should serve as a criterion for the evaluation of the individual renal function should be the one showing the poorest return. The phenolsulphonphthalein test should be used instead of "K" only in cases in which it is materially impossible to perform the latter; but, on the other hand, the results of "K" should always be controlled by a phenolsulphonphthalein test. Both tests complement each other, and their individual clinical value increases when they are studied together.

[Ed. Note.—Ambard's coefficient is still sponsored by a number of internists and urologists, particularly in France. It is interesting to note that it is gradually being replaced by the much simpler and more accurate phenolsulphonphthalein test.]

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24. Hélouin: L'épreuve de la phénolsulfonephthaléne intraveineuse dans l'exploration fonctionnelle rénale, Presse méd. **1**:755-756 (June 16) 1926.

*(To be continued)*